Elsevier Editorial System(tm) for Journal of Heart and Lung Transplantation
Manuscript Draft

Manuscript Number: JHLT-D-13-00499R2

Title: HEART TRANSPLANTATION IN PATIENTS WITH EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS SYNDROME)

Article Type: Original Clinical Science

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***Author Response comments**

Dear Dr Mandeep R. Mehra and Dr Patricia Uber,

Please find attached our revised manuscript (no. JHLT-D-13-00499) entitled, HEART TRANSPLANTATION IN PATIENTS WITH EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG–STRAUSS SYNDROME), by M Groh, G Masciocco, E Kirchner, et al, that we are resubmitting for publication as an Original Research Communication in the *Journal of Heart and Lung Transplantation*.

We sincerely thank the Editorial Board members for their support of our paper and Reviewer 1 for his/her time and pertinent remarks**.** Our detailed responses to the latter and the corresponding changes made in the text are given below. In the highlighted revised text, the deletions are double-barred and additions are in red.

The total word count after modification is now 2526, with 2 references deleted, for a total of 49 references in the revised manuscript.

We hope that these changes have helped clarify the issues raised by the Reviewer and that you will find the revised manuscript acceptable for publication in the *Journal of Heart and Lung Transplantation*.

We thank you in advance for your consideration and look forward to hearing from you soon.

Sincerely yours,

Matthieu Groh, MD

REVIEWER 1

Thus, I would suggest, if possible, to try making the paper more concise, taking advantage of the supplementary material, and focusing on the main messages that this important report bear:

We fully agree with the Reviewer's approach. Therefore, in the Results (pages 8 and 9–10), we deleted the information in the text that merely collated details given in Tables 1 and 4. In the Discussion (pages 11–12), we deleted the text that would be evident for transplant physicians and shortened the paragraph on connective diseases to facilitate reading and not cloud our messages.

I would put more emphasis on the finding that no myocardial relapse was demonstrated in the post-transplant EMBs, except for the only case in which autopsy was performed.

As mentioned in the online case series (page 2, second paragraph, lines 2–5), eosinophils suggestive of EGPA relapse were found in one of patient 1's post-transplant EMBs (concomitant with an atrial fibrillation episode). Thus, evidence suggests that at least 2 patients had post-transplant myocardial EGPA relapse.

Did the EGPA scores improve after transplant? At page 10 of the revised version, authors report the differences in VDI scores in survivors vs. non survivors, indirectly suggesting that those who died had more pronounced signs of disease relapse.

The vasculitis damage index records organ damage and sequelae that have occurred since the onset of vasculitis. Thus, this score can only rise during the course of the disease. In this series, the patients with the highest VDI scores (i.e., patients 2, 5, 6 and 8), most presumably because they have had the longest disease courses, are all still alive.

Finally, I still believe that the statement "EGPA patients with heart transplants could be considered at high risk for arrhythmias" an over interpretation. First, it must be considered that arrhythmic risk after transplant is related to rejection and/or to CAV. Often "sudden" death in patients with CAV or rejection is associated with pulseless electric activity, and with AV blocks, rather than VT/TV. Then, pre-transplant VT/TV episodes in patients 1,2,6, and 7 (page 12) cannot be considered as risk factors for post-transplant VT/TV. Finally, in any cardiac death the final mechanism of death is related to an inadequate electric activity, and thus is "arrhythmic". But this does not support the concept of "increased arrhythmic death".

We concur with the Reviewer's opinion. Hence, statements suggesting that EGPA patients might be at higher risk of arrhythmia have been deleted from the Abstract (page 3, paragraph

4, lines 5–6) and the Discussion (page 12, fourth paragraph, lines 5–9) sections.

Just a final brief comment on case 3: the likelihood that a patient dying with abdominal pain few days after a steroid load is due to rejection is as high as the likelihood that a cobra entered the bed and bit her.

We fully agree with this comment. The Online Supplemental Material document has been modified (page 4, first paragraph, lines 4–7).

A minor final comment, I think that the term "engraftment" may be more appropriately substituted by "transplant".

The manuscript has been modified (page 11, second paragraph, line 2) accordingly.

Supplemental tables with rejection grades may be redundant for JHLT readership.

As suggested, the tables with rejection grades have been deleted from the Online Supplemental Material and table 3's legend has been modified accordingly.

HEART TRANSPLANTATION IN PATIENTS WITH EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG–STRAUSS SYNDROME)

Type of article

Original Research Communication

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Total word count

2526 (including abstract but excluding references and figure legends).

ABSTRACT

BACKGROUND: Heart involvement is the leading cause of death of patients with eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome) (EGPA) and is more frequent in antineutrophil cytoplasm antibody (ANCA)-negative patients. Post-transplant outcome has only been reported once.

METHODS: We conducted a retrospective international multicenter study. Patients satisfying the American College of Rheumatology and/or revised Chapel Hill Consensus Conference Nomenclature criteria were identified by collaborating vasculitis and transplant specialists, and the help of the Churg–Strauss Syndrome Association.

RESULTS: Nine ANCA$^-$ patients who received transplants between October 1987 and December 2009 were identified. The vasculitis and cardiomyopathy diagnoses were concomitant for 5 patients and separated by 12–288 months for the remaining 4. Despite ongoing immunosuppression, histologic examination of 7 (78%) patients' explanted hearts showed histologic patterns suggestive of active vasculitis. The overall 5-year survival rate was low (57%) but rose to 80% when considering only the 6 patients transplanted during the last decade. After survival lasting 3–60 months, 4 (44%) patients died sudden deaths.

CONCLUSIONS: The search for EGPA-related cardiomyopathy is mandatory early during the course of this vasculitis. Indeed, prompt treatment with corticosteroids and cyclophosphamide may achieve recovery of cardiac function. Most patients in this series were undertreated. For patients with refractory EGPA, heart transplantation should be performed and carries a fair prognosis. No optimal immunosuppressive strategy has yet been identified. ~~Patients require close monitoring for arrhythmia post-transplantation.~~

KEYWORDS:

Churg–Strauss syndrome; hypereosinophilic syndrome; asthma; myocarditis; cardiomyopathy; heart transplantation; immunosuppression; cardiac arrhythmias

ABBREVIATIONS:

ANCA, antineutrophil cytoplasm antibodies; BVAS, Birmingham Vasculitis Activity Score; CAV, cardiac allograft vasculopathy; CMR, cell-mediated rejection; CMRI, cardiac magnetic resonance imaging; EGPA, eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); EMB, endomyocardial biopsy; ENT, ear, nose and throat; FFS, Five-Factor Score; ISHLT, International Society of Heart and Lung Transplantation; OHT, orthotopic heart transplantation; VDI, Vasculitis Damage Index.

Churg–Strauss syndrome, recently renamed eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) (EGPA),[1] is a rare systemic necrotizing vasculitis that affects small- and medium-sized arteries. Its prevalence is 7–13 cases/million inhabitants,[2-4] with an annual incidence of 0.5–6.8 new cases/million inhabitants.[5] Although its incidence is higher among asthmatic patients,[6,7] EGPA remains poorly known by most physicians. Its hallmark symptoms combine asthma, hypereosinophilia, systemic signs of vasculitis (especially mononeuritis multiplex) and anti-neutrophil cytoplasm antibodies (ANCAs) in 30–40% of the patients.[8-10]

Heart involvement occurs in approximately 8–20% of EGPA patients and is more frequent in ANCA$^-$ patients.[8,9,11] Because silent eosinophilic infiltration of the myocardium can remain subclinical, it is difficult to determine the true prevalence accurately. Moreover, the specificity of new imaging techniques (e.g. cardiac magnetic resonance imaging (CMRI) and fluoro-2-deoxyglucose positron-emission tomography) remains unclear.[12-15] Various histologic patterns (e.g., necrotizing vasculitis, eosinophil-rich inflammatory infiltrates, extravascular granuloma, coronary arteritis, intracavitary thrombus and/or endomyocardial fibrosis) and clinical manifestations (e.g., pericarditis, myocarditis, restrictive or dilated cardiomyopathy and arrhythmias) have been reported as EGPA-related cardiac disease.[12,16,17] Heart involvement, along with gastrointestinal, central nervous system and renal involvements, carries a poor prognosis and is part of the prognostic 1996 Five-Factor Score (FFS)[18] and the 2009 revisited FFS.[19] Pertinently, it is the leading cause of EGPA-associated deaths.[8,11] Because disease remission is not achieved for all patients and relapses are frequent,[20] the possibility of orthotopic heart transplantation (OHT) feasibility in patients with refractory EGPA arises.

Although the International Society for Heart and Lung Transplantation (ISHLT) does not consider systemic diseases contraindications for OHT,[21] an acute flare and/or a high risk of post-transplant disease recurrence often disqualifies patients from the procedure. Thus, according to some authors, EGPA is a limitation for OHT.[22] Herein, we describe the outcomes post-OHT of 9 patients with EGPA-related cardiomyopathy.

Methods

Patients

Patients satisfying the 1990 American College of Rheumatology criteria for EGPA[23] and/or the revised 2012 Chapel Hill Consensus Conference Nomenclature for EGPA[1] were identified by collaborating vasculitis and transplant specialists, with the help of the Churg–Strauss Syndrome Association. All living patients gave informed consent for data collection and analysis.

Assessments

Medical charts were retrieved and reviewed for demographic, clinical, biologic, radiologic and histologic findings at the time of EGPA and EGPA-related–cardiomyopathy diagnoses. Cardiomyopathy was diagnosed based on clinical findings in combination with electrocardiogram and transthoracic echocardiography, thereby corresponding to the FFS definition.[18] Pre-transplantation endomyocardial biopsies (EMBs) and histologic examination of explanted hearts were also noted as normal or showing signs of EGPA (e.g., vasculitis, granuloma, eosinophilic infiltrates), or non-specific histologic patterns (i.e., myocardial fibrosis or atheroma). Finally, post-transplant EMB were recorded as described above, in addition to the search for histologic evidence of cell (CMR)- and antibody-mediated rejections, in accordance with the different ISHLT guidelines in force at the time.[24-26]

Disease activity, severity and damage

Using the 2003 revised Birmingham Vasculitis Activity Score (BVAS),[27] the revisited FFS[19] and the Vasculitis Damage Index (VDI),[28] the vasculitis specialist retrospectively assessed disease activity, severity and damage. Briefly, the BVAS is a clinical index of disease activity comprising 56 items concerning 9 separate organ systems, which are scored (maximum score of 63) only if they are

attributable to active systemic necrotizing vasculitis. The FFS is a prognostic score that consists of 5 items (including heart involvement) significantly associated with poorer outcomes. When the FFS is ≥ 1, cyclophosphamide (or rituximab) combined with steroids is strongly recommended for ANCA-associated vasculitides induction therapy.[29] The VDI is a tool for evaluating organ damage that has occurred since the onset of vasculitis.[28]

Outcomes

Outcomes included EGPA relapses, post-transplant functional and working statuses at the last consultation, post-transplant complications and deaths. EGPA relapse was defined as 1) the recurrence or worsening of a clinical EGPA manifestation, after remission lasting ≥ 3 months, 2) requiring the addition or change of immunosuppressive drug(s) and/or the reinstitution of prednisone at a dose > 20 mg/day or an increase of the prednisone dose more than twice the previous dose and > 30 mg/day.[30] Increased eosinophil count without any other clinical EGPA manifestation and isolated asthma or sinusitis exacerbations (with or without concomitant eosinophil-count rise) necessitating therapeutic adjustments were not considered EGPA relapses but were analyzed separately.

Post-transplant complications comprised acute allograft rejection (CMR or antibody-mediated), cardiac allograft vasculopathy ((CAV), as defined by the ISHLT standardized nomenclature),[31] graft failure, infection, malignancy, chronic kidney disease, hypertension, diabetes mellitus, dyslipidemia and/or intensive care unit admission.

Results

Patients

Nine patients (4 women and 5 men), who underwent OHT for EGPA-related cardiomyopathy between October 1987 and December 2009 in 8 transplant centers in 6 different countries, were identified**.** Their case reports are available in the Online Supplemental Material. Parts of patient 7–9's medical histories were previously published[32-34] but only patient 9's post-transplant outcome has been reported.[22]

Table 1 summarizes the patients' characteristics at EGPA diagnosis, when their median age was 36 (range 22–62) years. All patients had asthma, lung infiltrates and ANCA$^-$ serology (ANCA serology was not available at the time of patient 9's EGPA diagnosis and no frozen serum was available for future analysis). ~~None had concomitant gastrointestinal, central nervous system, eye or renal involvements. All seven (78%) patients with ear, nose and throat (ENT) manifestations had sinusitis and/or polyposis. Six (67%) patients had arthralgias and 5 (56%) myalgias. Three (33%) patients had a lung nodule. Four (44%) patients had skin manifestations: 2 (22%) with subcutaneous nodules and 3 (33%) with purpura. Mean eosinophilia at diagnosis was 9.4 ± 4.9 eosinophils/ml.~~

EGPA-related cardiomyopathy

Table 2 summarizes the patients' characteristics at diagnosis of heart involvement. EGPA and cardiomyopathy were diagnosed concomitantly for 5 (56%) patients. For the 4 (44%) remaining patients, the interval between the 2 diagnoses was 12–288 months. All patients presented with severe acute eosinophilic myocarditis [respective median (range) troponin I and N-terminal prohormone of brain natriuretic peptide concentrations: 8.85 (0.012–19.6) μg/liter and 3841 (601–32,397) pg/ml], abnormal ECG and severely diminished left ventricular ejection fraction (mean 24 ± 6%) due to active EGPA (mean BVAS 35 ± 9). Seven (78%) patients had dilated cardiomyopathy but none had

ventricular hypertrophy. Intracavitary thromboses were detected in 3 (33%) patients with dilated cardiomyopathy. Two (22%) patients underwent CMRI, which was suggestive of active vasculitis in both cases (Figure 1). Six (67%) patients had coronary angiograms but only patient 2's was abnormal, revealing 40% stenosis of the anterior interventricular artery. BVAS at diagnosis of heart involvement ranged from 26 to 50 (mean 35 ± 9). The revised FFS equaled 1 point for 7 (78%) patients, and 2 points for patients 5 and 9, who had no ENT manifestations when cardiomyopathy was diagnosed.

Heart transplantation

The interval between EGPA-related–cardiomyopathy diagnosis and OHT was 2–15 (mean 9 ± 4.8) months. All heart transplants were ABO compatible and had negative cross matches.

Histologic findings

Table 3 summarizes histologic findings. Seven (78%) patients had an EMB before transplant. Five were abnormal (with an eosinophil-rich infiltrate being the leading pattern found), but only 2 had EGPA-specific histologic findings. Intriguingly, despite ongoing immunosuppression, 7 (78%) patients' explanted hearts still showed evidence of EGPA (Figure 2); among them, 6 (67%) had signs of active vasculitis. Six (67%) patients had non-specific histologic patterns with myocardial fibrosis being the most common.

Therapeutic regimens

All patients took corticosteroids before transplantation but only 5 (56%) were prescribed additional immunosuppressants and only 3 (33%) received cyclophosphamide pulses. Seven (78%) patients required vasoactive support and/or levosimendan pre-transplantation. Five (56%) patients had an intra-aortic balloon pump or ventricular heart-assist device during the pre-graft period.

Table 4 summarizes post-operative care of the OHT recipients, where the details of

cardioactive treatments are available for 8 of the 9 patients. ~~Seven (78%) patients received induction therapy, with antithymoglobulins being given to 5. Cyclosporine was the preferred calcineurin inhibitor, prescribed to 8 (89%) patients, whereas tacrolimus first-line therapy was given to only 1 (11%). Patient 5 was switched from cyclosporine to everolimus because of chronic kidney disease, and patient 6 from cyclosporine to tacrolimus after a grade 1B CMR. Azathioprine was the preferred first-line anti-purine, prescribed to 6 (67%) patients, while mycophenolate mofetil was started in 3 (33%). Patients 1 and 2 were switched from azathioprine to mycophenolate mofetil to treat EGPA relapse and toxidermia, respectively. Patient 5 was switched from mycophenolate mofetil to azathioprine to counter gastrointestinal intolerance.~~

Post-transplant outcomes

Of the 9 patients in this series, 4 (44%) died, all suddenly, with post-transplant survival lasting 3–60 (mean 32 ± 29) months (Table 4). Follow-up for the 5 (56%) survivors was 55–102 (mean 74 ± 23) months, at this writing. At the last medical visit, VDI range was 0–2 (mean 1 ± 1) for the non-survivors and 0–9 (mean 4.6 ± 3.6) for the survivors. Three (33%) patients experienced EGPA relapses, with the transplant-to-first-relapse interval lasting 2–48 months. Three (33%) additional patients suffered post-graft asthma and/or sinusitis flares that required increased corticosteroid doses.

All patients experienced post-transplant complications. Infection and CMR were the most frequent, occurring in 6 (67%) patients each. The transplant-to-heart-rejection interval ranged from 1 to 74 (mean 23 ± 28) months. No graft failure or malignancy was reported. Lastly, only 3 (38%) patients reported some activity limitations and none required assistance for daily life activities.

Discussion

The clinical phenotypes of ANCA$^+$ and ANCA$^-$ EGPA patients differ.[8-10] ANCA$^+$ patients have a vasculitic phenotype, with more frequent glomerulonephritis, mononeuritis multiplex and relapses. Although ANCA$^-$ patients have fewer relapses, they have poorer prognoses, presumably because they have more frequent cardiomyopathy.[8,11] According to multivariate analysis, heart involvement is the strongest independent predictor of EGPA-attributable mortality.[8] Notably, all patients in this series were ANCA$^-$, which is consistent with previously published data on EGPA-related heart involvement.[8,9,12,15] Despite the low number of patients considered herein, several other pertinent observations can be made.

First, most patients were undertreated and transplanted while their EGPA was active. Indeed, only 3 patients received cyclophosphamide pulses before ~~engraftment~~ transplant and, despite ongoing immunosuppression, 6 patients' explanted hearts showed histologic patterns of active vasculitis. Physicians should be aware that, because it is life-threatening, EGPA cardiac involvement must be identified early during the course of this vasculitis and that it requires immediate therapy with corticosteroids and cyclophosphamide pulses, which may achieve recovery of cardiac function.[35,36] Pertinently, both patients without histologic evidence of cardiac EGPA received early corticosteroid therapy and pulse cyclophosphamide, thereby highlighting that an aggressive immunosuppressive strategy might induce vasculitis remission pre-transplantation. In addition, it is highly likely that patient 2 and 6's initial symptoms were already EGPA-related cardiac manifestations but, unfortunately, they were not immediately diagnosed as such. We recommend complementary cardiac investigations for EGPA patients (especially those ANCA$^-$) not only to properly evaluate symptomatic patients but, above all, to detect cardiac involvement in asymptomatic patients. CMRI seems to be more sensitive than echocardiography for this assessment but its specificity remains unclear.[12-14] In addition to diagnostic imaging, and as recommended by the European Society of Cardiology, American Heart Association and American College of Cardiology Foundation,[37] EMB should be obtained from patients with unexplained heart failure associated with eosinophilia, ideally before starting immunosuppressants.

Second, OHT is feasible in patients with refractory EGPA and carries a fair prognosis. Although the overall 5-year post-transplant survival rate was low (57%), it rose to 80% when we considered only the 6 patients (i.e. patients 1, 2, 4, 5, 7 and 8) transplanted during the last decade. These data are in agreement with recent findings showing that post-transplant survival of patients with pre-transplant hypersensitivity myocarditis (which shares some common histologic patterns with EGPA)[38] or lymphocytic myocarditis[39] was the same (albeit with more frequent late CMRs) as that of patients transplanted for other causes.

Unfortunately, data on OHT in patients with other systemic diseases are very scarce.[40-43] ~~So far, only 8 systemic lupus erythematosus patients who underwent OHT have been reported.[40] Six had fair outcomes (follow-up lasting up to 4 years) but 2 with secondary anti-phospholipid syndrome died of thrombosis. Moreover, OHT in only 1 patient with rheumatoid and dilated cardiomyopathy has been published.[41] Lastly, although lung transplantation has been described in several patients with systemic sclerosis,[42] the first OHT in this setting was reported only recently.[43]~~ Generally speaking, for patients with systemic diseases, an individualized approach, considering cardiac disease severity, the likelihood of underlying disease relapse post-transplantation and the presence of other comorbidities, seems reasonable. Ideally, EGPA patients should undergo transplantation after corticosteroids and pulse cyclophosphamide induction has achieved vasculitis remission.

~~Evidently, OHT in this setting should also follow the ISHLT guidelines for the management of heart transplant recipients.[44] Among others, patients should be strictly monitored for cardiovascular risk factors, receive antimicrobial prophylaxis to reduce the risks of cytomegalovirus and protozoan infections, and take statins to prevent CAV.~~

Third, although OHT is feasible in EGPA, some patients had poor outcomes and 4 died sudden deaths. Postmortem examination of patient 9's transplanted heart showed severe CAV, CMR and EGPA relapse. Unfortunately, the 3 other patients were not autopsied. Thus, we can only speculate about the causes of their deaths but acute arrhythmia due to CAV, myocardial fibrosis, vasculitis relapse and/or graft rejections are plausible explanations. ~~Furthermore, ventricular tachycardia and/or ventricular fibrillation episodes were recorded pre-engraftment in patients 1, 2, 6 and 7, and recent findings suggest that patients with non-ischemic cardiomyopathy and ventricular~~

~~tachycardia have extensive myocardial scars, which can lead to arrhythmia.[45] Thus, EGPA patients with heart transplants could be considered at high risk for arrhythmias.~~

Fourth, the absence of an optimal immunosuppressive strategy might have had a negative impact on the patients' outcomes. ~~Although post-transplant induction therapy remains controversial, it could be beneficial for patients at high risk for acute rejection and/or renal dysfunction.[44] Moreover, to date, information is insufficient to recommend anti-interleukin-2 receptor antibodies or antithymoglobulins.[46]~~ Maintenance therapy after OHT combines a calcineurin inhibitor with an anti-purine or a proliferation-signal inhibitor. Recent findings suggest that tacrolimus is superior to microemulsion cyclosporine with regard to acute severe biopsy-proven rejection,[44] hypertension, hyperlipidemia, viral infections and CAV.[45] Unfortunately, information on tacrolimus use in EGPA is scarce.[46] ~~Notably, only patient 8 received first-line tacrolimus and has had no EGPA flares and is doing well 6 years post-OHT.~~ Azathioprine was the preferred first-line anti-purine. However, recent observations showed that post-transplant use of azathioprine rather than mycophenolate mofetil or mycophenolic acid increased the risk of CAV, malignancy and/or death.[47] Unlike other ANCA-associated vasculitides,[48] no data are available comparing azathioprine vs mycophenolate mofetil as EGPA maintenance therapy. Lastly, the ISHLT recommends corticosteroid withdrawal 3–6 months after transplant for low-risk patients,[49] but that goal seems difficult to achieve in EGPA patients who often require persistent low-dose corticosteroids to control their asthma. Furthermore, standard post-transplant immunosuppressive therapy was unable to control EGPA in some patients. Indeed, 6 patients' EGPA relapsed or they experienced asthma flares, requiring higher corticosteroid doses than those routinely used in heart-transplant recipients. Therefore, in this setting, we recommend using an aggressive immunosuppressive protocol to avoid graft rejection and disease progression. Nevertheless, immunosuppression should be tailored individually.

Finally, taking into account the possibility of late rejection and/or EGPA relapse, indefinite surveillance with a yearly EMB is probably reasonable. However, individual considerations, the risk of the procedure and the reduced diagnostic yield of repeated EMBs might plead for a less invasive approach, perhaps 2 years after transplantation. The latter could comprise strict monitoring of inflammatory parameters and eosinophil activation, dosage of myocardial necrosis markers, non-

invasive approaches for the diagnosis of acute cardiac allograft rejection, donor-specific antibody monitoring, and cardiac function evaluation with repeated echocardiography and/or CMRI (which can also be useful to guide the need for EMB).

While this study brings new findings to light, its limitations include the retrospective design and the small number of EGPA patients worldwide who have received heart transplants. OHT in EGPA is a very rare situation and more data are needed to improve patient care.

Disclosure statement

No funding was received for this study and the authors have no conflicts of interest to disclose.

Acknowledgments

The authors would like to thank Jane Dion for data collection, Cloé Comarmond, Christian Pagnoux and Marion Marquardt for their helpful comments, and Janet Jacobson for editorial assistance.

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Figure legends

Figure 1. Cardiac magnetic resonance imaging of patient 2. (A) Short-axis view of 3-dimensional delayed-enhancement T1-weighted gradient-echo inversion-recovery magnetic resonance image (repetition time: 1.4 ms; echo time: 600 ms; inversion time: 250 ms) showing septal myocardial delayed enhancement (arrow). (B) Short-axis view of 2-dimensional inversion recovery, black blood fast spin-echo image (repetition time: 700 ms; echo time: 47 ms; inversion time: 170 ms) showing septal myocardial T2-weighted hyperintensity (arrow) consistent with edema.

Figure 2. Histopathologic examination of patient 1's explanted heart. (A) Cardiectomy: high-grade bi-ventricular dilation with myocardial fibrosis and focal areas of macroscopic interstitial fibrosis (arrows) unrelated to coronary territory. (B) Interstitial focus of fibrinoid necrosis (A) encircled by epithelioid histiocytes, a giant cell (B), eosinophils (C) and lymphocytes (§). Hematoxylin-and-eosin stain, × 200.

HEART TRANSPLANTATION IN PATIENTS WITH EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG–STRAUSS SYNDROME)

Type of article

Original Research Communication

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Total word count

2526 (including abstract but excluding references and figure legends).

ABSTRACT

BACKGROUND: Heart involvement is the leading cause of death of patients with eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome) (EGPA) and is more frequent in antineutrophil cytoplasm antibody (ANCA)-negative patients. Post-transplant outcome has only been reported once.

METHODS: We conducted a retrospective international multicenter study. Patients satisfying the American College of Rheumatology and/or revised Chapel Hill Consensus Conference Nomenclature criteria were identified by collaborating vasculitis and transplant specialists, and the help of the Churg–Strauss Syndrome Association.

RESULTS: Nine ANCA$^-$ patients who received transplants between October 1987 and December 2009 were identified. The vasculitis and cardiomyopathy diagnoses were concomitant for 5 patients and separated by 12–288 months for the remaining 4. Despite ongoing immunosuppression, histologic examination of 7 (78%) patients' explanted hearts showed histologic patterns suggestive of active vasculitis. The overall 5-year survival rate was low (57%) but rose to 80% when considering only the 6 patients transplanted during the last decade. After survival lasting 3–60 months, 4 (44%) patients died sudden deaths.

CONCLUSIONS: The search for EGPA-related cardiomyopathy is mandatory early during the course of this vasculitis. Indeed, prompt treatment with corticosteroids and cyclophosphamide may achieve recovery of cardiac function. Most patients in this series were undertreated. For patients with refractory EGPA, heart transplantation should be performed and carries a fair prognosis. No optimal immunosuppressive strategy has yet been identified.

KEYWORDS:

Churg–Strauss syndrome; hypereosinophilic syndrome; asthma; myocarditis; cardiomyopathy; heart transplantation; immunosuppression; cardiac arrhythmias

ABBREVIATIONS:

ANCA, antineutrophil cytoplasm antibodies; BVAS, Birmingham Vasculitis Activity Score; CAV, cardiac allograft vasculopathy; CMR, cell-mediated rejection; CMRI, cardiac magnetic resonance imaging; EGPA, eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); EMB, endomyocardial biopsy; ENT, ear, nose and throat; FFS, Five-Factor Score; ISHLT, International Society of Heart and Lung Transplantation; OHT, orthotopic heart transplantation; VDI, Vasculitis Damage Index.

Churg–Strauss syndrome, recently renamed eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) (EGPA),[1] is a rare systemic necrotizing vasculitis that affects small- and medium-sized arteries. Its prevalence is 7–13 cases/million inhabitants,[2-4] with an annual incidence of 0.5–6.8 new cases/million inhabitants.[5] Although its incidence is higher among asthmatic patients,[6,7] EGPA remains poorly known by most physicians. Its hallmark symptoms combine asthma, hypereosinophilia, systemic signs of vasculitis (especially mononeuritis multiplex) and anti-neutrophil cytoplasm antibodies (ANCAs) in 30–40% of the patients.[8-10]

Heart involvement occurs in approximately 8–20% of EGPA patients and is more frequent in ANCA$^-$ patients.[8,9,11] Because silent eosinophilic infiltration of the myocardium can remain subclinical, it is difficult to determine the true prevalence accurately. Moreover, the specificity of new imaging techniques (e.g. cardiac magnetic resonance imaging (CMRI) and fluoro-2-deoxyglucose positron-emission tomography) remains unclear.[12-15] Various histologic patterns (e.g., necrotizing vasculitis, eosinophil-rich inflammatory infiltrates, extravascular granuloma, coronary arteritis, intracavitary thrombus and/or endomyocardial fibrosis) and clinical manifestations (e.g., pericarditis, myocarditis, restrictive or dilated cardiomyopathy and arrhythmias) have been reported as EGPA-related cardiac disease.[12,16,17] Heart involvement, along with gastrointestinal, central nervous system and renal involvements, carries a poor prognosis and is part of the prognostic 1996 Five-Factor Score (FFS)[18] and the 2009 revisited FFS.[19] Pertinently, it is the leading cause of EGPA-associated deaths.[8,11] Because disease remission is not achieved for all patients and relapses are frequent,[20] the possibility of orthotopic heart transplantation (OHT) feasibility in patients with refractory EGPA arises.

Although the International Society for Heart and Lung Transplantation (ISHLT) does not consider systemic diseases contraindications for OHT,[21] an acute flare and/or a high risk of post-transplant disease recurrence often disqualifies patients from the procedure. Thus, according to some authors, EGPA is a limitation for OHT.[22] Herein, we describe the outcomes post-OHT of 9 patients with EGPA-related cardiomyopathy.

Methods

Patients

Patients satisfying the 1990 American College of Rheumatology criteria for EGPA[23] and/or the revised 2012 Chapel Hill Consensus Conference Nomenclature for EGPA[1] were identified by collaborating vasculitis and transplant specialists, with the help of the Churg–Strauss Syndrome Association. All living patients gave informed consent for data collection and analysis.

Assessments

Medical charts were retrieved and reviewed for demographic, clinical, biologic, radiologic and histologic findings at the time of EGPA and EGPA-related–cardiomyopathy diagnoses. Cardiomyopathy was diagnosed based on clinical findings in combination with electrocardiogram and transthoracic echocardiography, thereby corresponding to the FFS definition.[18] Pre-transplantation endomyocardial biopsies (EMBs) and histologic examination of explanted hearts were also noted as normal or showing signs of EGPA (e.g., vasculitis, granuloma, eosinophilic infiltrates), or non-specific histologic patterns (i.e., myocardial fibrosis or atheroma). Finally, post-transplant EMB were recorded as described above, in addition to the search for histologic evidence of cell (CMR)- and antibody-mediated rejections, in accordance with the different ISHLT guidelines in force at the time.[24-26]

Disease activity, severity and damage

Using the 2003 revised Birmingham Vasculitis Activity Score (BVAS),[27] the revisited FFS[19] and the Vasculitis Damage Index (VDI),[28] the vasculitis specialist retrospectively assessed disease activity, severity and damage. Briefly, the BVAS is a clinical index of disease activity comprising 56 items concerning 9 separate organ systems, which are scored (maximum score of 63) only if they are

attributable to active systemic necrotizing vasculitis. The FFS is a prognostic score that consists of 5 items (including heart involvement) significantly associated with poorer outcomes. When the FFS is ≥ 1, cyclophosphamide (or rituximab) combined with steroids is strongly recommended for ANCA-associated vasculitides induction therapy.[29] The VDI is a tool for evaluating organ damage that has occurred since the onset of vasculitis.[28]

Outcomes

Outcomes included EGPA relapses, post-transplant functional and working statuses at the last consultation, post-transplant complications and deaths. EGPA relapse was defined as 1) the recurrence or worsening of a clinical EGPA manifestation, after remission lasting ≥ 3 months, 2) requiring the addition or change of immunosuppressive drug(s) and/or the reinstitution of prednisone at a dose > 20 mg/day or an increase of the prednisone dose more than twice the previous dose and > 30 mg/day.[30] Increased eosinophil count without any other clinical EGPA manifestation and isolated asthma or sinusitis exacerbations (with or without concomitant eosinophil-count rise) necessitating therapeutic adjustments were not considered EGPA relapses but were analyzed separately.

Post-transplant complications comprised acute allograft rejection (CMR or antibody-mediated), cardiac allograft vasculopathy ((CAV), as defined by the ISHLT standardized nomenclature),[31] graft failure, infection, malignancy, chronic kidney disease, hypertension, diabetes mellitus, dyslipidemia and/or intensive care unit admission.

Results

Patients

Nine patients (4 women and 5 men), who underwent OHT for EGPA-related cardiomyopathy between October 1987 and December 2009 in 8 transplant centers in 6 different countries, were identified**.** Their case reports are available in the Online Supplemental Material. Parts of patient 7–9's medical histories were previously published[32-34] but only patient 9's post-transplant outcome has been reported.[22]

Table 1 summarizes the patients' characteristics at EGPA diagnosis, when their median age was 36 (range 22–62) years. All patients had asthma, lung infiltrates and $ANCA^-$ serology (ANCA serology was not available at the time of patient 9's EGPA diagnosis and no frozen serum was available for future analysis).

EGPA-related cardiomyopathy

Table 2 summarizes the patients' characteristics at diagnosis of heart involvement. EGPA and cardiomyopathy were diagnosed concomitantly for 5 (56%) patients. For the 4 (44%) remaining patients, the interval between the 2 diagnoses was 12–288 months. All patients presented with severe acute eosinophilic myocarditis [respective median (range) troponin I and N-terminal prohormone of brain natriuretic peptide concentrations: 8.85 (0.012–19.6) μg/liter and 3841 (601–32,397) pg/ml], abnormal ECG and severely diminished left ventricular ejection fraction (mean 24 ± 6%) due to active EGPA (mean BVAS 35 ± 9). Seven (78%) patients had dilated cardiomyopathy but none had ventricular hypertrophy. Intracavitary thromboses were detected in 3 (33%) patients with dilated cardiomyopathy. Two (22%) patients underwent CMRI, which was suggestive of active vasculitis in both cases (Figure 1). Six (67%) patients had coronary angiograms but only patient 2's was abnormal, revealing 40% stenosis of the anterior interventricular artery. BVAS at diagnosis of heart involvement

ranged from 26 to 50 (mean 35 ± 9). The revised FFS equaled 1 point for 7 (78%) patients, and 2 points for patients 5 and 9, who had no ENT manifestations when cardiomyopathy was diagnosed.

Heart transplantation

The interval between EGPA-related–cardiomyopathy diagnosis and OHT was 2–15 (mean 9 ± 4.8) months. All heart transplants were ABO compatible and had negative cross matches.

Histologic findings

Table 3 summarizes histologic findings. Seven (78%) patients had an EMB before transplant. Five were abnormal (with an eosinophil-rich infiltrate being the leading pattern found), but only 2 had EGPA-specific histologic findings. Intriguingly, despite ongoing immunosuppression, 7 (78%) patients' explanted hearts still showed evidence of EGPA (Figure 2); among them, 6 (67%) had signs of active vasculitis. Six (67%) patients had non-specific histologic patterns with myocardial fibrosis being the most common.

Therapeutic regimens

All patients took corticosteroids before transplantation but only 5 (56%) were prescribed additional immunosuppressants and only 3 (33%) received cyclophosphamide pulses. Seven (78%) patients required vasoactive support and/or levosimendan pre-transplantation. Five (56%) patients had an intra-aortic balloon pump or ventricular heart-assist device during the pre-graft period.

Table 4 summarizes post-operative care of the OHT recipients, where the details of cardioactive treatments are available for 8 of the 9 patients.

Post-transplant outcomes

Of the 9 patients in this series, 4 (44%) died, all suddenly, with post-transplant survival lasting 3–60 (mean 32 ± 29) months (Table 4). Follow-up for the 5 (56%) survivors was 55–102 (mean 74 ± 23) months, at this writing. At the last medical visit, VDI range was 0–2 (mean 1 ± 1) for the non-survivors and 0–9 (mean 4.6 ± 3.6) for the survivors. Three (33%) patients experienced EGPA relapses, with the transplant-to-first-relapse interval lasting 2–48 months. Three (33%) additional patients suffered post-graft asthma and/or sinusitis flares that required increased corticosteroid doses.

All patients experienced post-transplant complications. Infection and CMR were the most frequent, occurring in 6 (67%) patients each. The transplant-to-heart-rejection interval ranged from 1 to 74 (mean 23 ± 28) months. No graft failure or malignancy was reported. Lastly, only 3 (38%) patients reported some activity limitations and none required assistance for daily life activities.

Discussion

The clinical phenotypes of ANCA$^+$ and ANCA$^-$ EGPA patients differ.[8-10] ANCA$^+$ patients have a vasculitic phenotype, with more frequent glomerulonephritis, mononeuritis multiplex and relapses. Although ANCA$^-$ patients have fewer relapses, they have poorer prognoses, presumably because they have more frequent cardiomyopathy.[8,11] According to multivariate analysis, heart involvement is the strongest independent predictor of EGPA-attributable mortality.[8] Notably, all patients in this series were ANCA$^-$, which is consistent with previously published data on EGPA-related heart involvement.[8,9,12,15] Despite the low number of patients considered herein, several other pertinent observations can be made.

First, most patients were undertreated and transplanted while their EGPA was active. Indeed, only 3 patients received cyclophosphamide pulses before transplant and, despite ongoing immunosuppression, 6 patients' explanted hearts showed histologic patterns of active vasculitis. Physicians should be aware that, because it is life-threatening, EGPA cardiac involvement must be identified early during the course of this vasculitis and that it requires immediate therapy with corticosteroids and cyclophosphamide pulses, which may achieve recovery of cardiac function.[35,36] Pertinently, both patients without histologic evidence of cardiac EGPA received early corticosteroid therapy and pulse cyclophosphamide, thereby highlighting that an aggressive immunosuppressive strategy might induce vasculitis remission pre-transplantation. In addition, it is highly likely that patient 2 and 6's initial symptoms were already EGPA-related cardiac manifestations but, unfortunately, they were not immediately diagnosed as such. We recommend complementary cardiac investigations for EGPA patients (especially those ANCA$^-$) not only to properly evaluate symptomatic patients but, above all, to detect cardiac involvement in asymptomatic patients. CMRI seems to be more sensitive than echocardiography for this assessment but its specificity remains unclear.[12-14] In addition to diagnostic imaging, and as recommended by the European Society of Cardiology, American Heart Association and American College of Cardiology Foundation,[37] EMB should be obtained from patients with unexplained heart failure associated with eosinophilia, ideally before starting immunosuppressants.

Second, OHT is feasible in patients with refractory EGPA and carries a fair prognosis. Although the overall 5-year post-transplant survival rate was low (57%), it rose to 80% when we considered only the 6 patients (i.e. patients 1, 2, 4, 5, 7 and 8) transplanted during the last decade. These data are in agreement with recent findings showing that post-transplant survival of patients with pre-transplant hypersensitivity myocarditis (which shares some common histologic patterns with EGPA)[38] or lymphocytic myocarditis[39] was the same (albeit with more frequent late CMRs) as that of patients transplanted for other causes.

Unfortunately, data on OHT in patients with other systemic diseases are very scarce.[40-43] Generally speaking, for patients with systemic diseases, an individualized approach, considering cardiac disease severity, the likelihood of underlying disease relapse post-transplantation and the presence of other comorbidities, seems reasonable. Ideally, EGPA patients should undergo transplantation after corticosteroids and pulse cyclophosphamide induction has achieved vasculitis remission.

Third, although OHT is feasible in EGPA, some patients had poor outcomes and 4 died sudden deaths. Postmortem examination of patient 9's transplanted heart showed severe CAV, CMR and EGPA relapse. Unfortunately, the 3 other patients were not autopsied. Thus, we can only speculate about the causes of their deaths but acute arrhythmia due to CAV, myocardial fibrosis, vasculitis relapse and/or graft rejections are plausible explanations.

Fourth, the absence of an optimal immunosuppressive strategy might have had a negative impact on the patients' outcomes. Maintenance therapy after OHT combines a calcineurin inhibitor with an anti-purine or a proliferation-signal inhibitor. Recent findings suggest that tacrolimus is superior to microemulsion cyclosporine with regard to acute severe biopsy-proven rejection,[44] hypertension, hyperlipidemia, viral infections and CAV.[45] Unfortunately, information on tacrolimus use in EGPA is scarce. Azathioprine was the preferred first-line anti-purine. However, recent observations showed that post-transplant use of azathioprine rather than mycophenolate mofetil or mycophenolic acid increased the risk of CAV, malignancy and/or death.[47] Unlike other ANCA-associated vasculitides,[48] no data are available comparing azathioprine vs mycophenolate mofetil as EGPA maintenance therapy. Lastly, the ISHLT recommends corticosteroid withdrawal 3–6 months

after transplant for low-risk patients,[49] but that goal seems difficult to achieve in EGPA patients who often require persistent low-dose corticosteroids to control their asthma. Furthermore, standard post-transplant immunosuppressive therapy was unable to control EGPA in some patients. Indeed, 6 patients' EGPA relapsed or they experienced asthma flares, requiring higher corticosteroid doses than those routinely used in heart-transplant recipients. Therefore, in this setting, we recommend using an aggressive immunosuppressive protocol to avoid graft rejection and disease progression. Nevertheless, immunosuppression should be tailored individually.

Finally, taking into account the possibility of late rejection and/or EGPA relapse, indefinite surveillance with a yearly EMB is probably reasonable. However, individual considerations, the risk of the procedure and the reduced diagnostic yield of repeated EMBs might plead for a less invasive approach, perhaps 2 years after transplantation. The latter could comprise strict monitoring of inflammatory parameters and eosinophil activation, dosage of myocardial necrosis markers, non-invasive approaches for the diagnosis of acute cardiac allograft rejection, donor-specific antibody monitoring, and cardiac function evaluation with repeated echocardiography and/or CMRI (which can also be useful to guide the need for EMB).

While this study brings new findings to light, its limitations include the retrospective design and the small number of EGPA patients worldwide who have received heart transplants. OHT in EGPA is a very rare situation and more data are needed to improve patient care.

Disclosure statement

No funding was received for this study and the authors have no conflicts of interest to disclose.

Acknowledgments

The authors would like to thank Jane Dion for data collection, Cloé Comarmond, Christian Pagnoux and Marion Marquardt for their helpful comments, and Janet Jacobson for editorial assistance.

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Figure legends

Figure 1. Cardiac magnetic resonance imaging of patient 2. (A) Short-axis view of 3-dimensional delayed-enhancement T1-weighted gradient-echo inversion-recovery magnetic resonance image (repetition time: 1.4 ms; echo time: 600 ms; inversion time: 250 ms) showing septal myocardial delayed enhancement (arrow). (B) Short-axis view of 2-dimensional inversion recovery, black blood fast spin-echo image (repetition time: 700 ms; echo time: 47 ms; inversion time: 170 ms) showing septal myocardial T2-weighted hyperintensity (arrow) consistent with edema.

Figure 2. Histopathologic examination of patient 1's explanted heart. (A) Cardiectomy: high-grade bi-ventricular dilation with myocardial fibrosis and focal areas of macroscopic interstitial fibrosis (arrows) unrelated to coronary territory. (B) Interstitial focus of fibrinoid necrosis (A) encircled by epithelioid histiocytes, a giant cell (B), eosinophils (C) and lymphocytes (§). Hematoxylin-and-eosin stain, × 200.

ABBREVIATIONS

AMR, antibody-mediated rejection; ANCA, antineutrophil cytoplasm antibodies; CAV, cardiac allograft vasculopathy; CHF, congestive heart failure; CMRI, cardiac magnetic resonance imaging; CMR, cell-mediated rejection; CMV, cytomegalovirus; CT, computed tomography; EGPA, eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); EMB, endomyocardial biopsy; ENT = ear, nose and throat; IABP, intra-aortic balloon pump; HLA, human lymphocyte antigen; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MF, myocardial fibrosis; OHT, orthotopic heart transplantation.

CASE REPORTS

Case 1

A woman born in 1955 was diagnosed with eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) (EGPA) in 1985 based on asthma, differential white-blood-cell–count eosinophilia, non-fixed pulmonary infiltrates, chronic paranasal sinus pain, skin biopsy showing perivascular inflammation with dense eosinophilic infiltrate and giant-cell granuloma in a context of arthralgias and pericarditis. Antineutrophil cytoplasm antibody (ANCA) serology was negative. Various treatments including azathioprine, methotrexate, cyclosporine and mycophenolate mofetil were administered until 2009. During those years, she had many relapses, and successively developed polyneuritis, retro-tympanic granuloma and eosinophilic gastroenteritis, while control of her asthma required continuous corticosteroids.

In 2009, mitral regurgitation and severe dilated cardiomyopathy with left ventricular ejection fraction (LVEF) estimated at 33% were diagnosed. Coronary angiogram was normal. Despite cardioactive treatment, several episodes of acute congestive heart failure (CHF) and an episode of ventricular tachycardia treated with amiodarone occurred. Orthotopic heart transplantation (OHT) was performed in December 2009 in Niguarda Ca' Granda Hospital in Milan, Italy. Histopathologic examination of the explanted heart found extensive myocardial fibrosis (MF), fibrinoid necrosis and

an eosinophil-rich infiltrate (Figure 2). Outcome was favorable with immunosuppressive therapy (cyclosporine 175 mg bid, and azathioprine 75 mg/day enabling prednisone tapering), cardioactive therapy (atenolol 25 mg/day, ramipril 2.5 mg/day, aspirin 100 mg/day, and simavastatin 20 mg/day) and anti-cytomegalovirus (CMV) prophylaxis (valganciclovir 450 mg/day).

In February 2010, the patient developed atrial fibrillation, which was successfully treated with electrical cardioversion. Endomyocardial biopsy (EMB) showed a mixed acute cell (CMR)- and antibody-mediated rejections (AMR) (graded 1R and pAMR2, respectively; see Tables S1 and S2for explanations of acute CMR and AMR gradings) and eosinophilic granulocytes suggestive EGPA recurrence. Her health improved with intravenous immunoglobulins (25 g/day for 5 days) and pulse corticosteroids. Methotrexate (15 mg/week) was started and azathioprine was replaced by mycophenolate mofetil (550 mg bid). Since then, all EMBs have been normal.

In July 2011, despite the absence of clinical or biologic signs of EGPA activity, the patient died suddenly. No autopsy was performed.

Case 2

In July 2007, a 52-year-old man, with a 3-year history of asthma and a CHF episode with normal coronary angiogram 3 years earlier, was diagnosed with EGPA: late asthma, non-fixed pulmonary infiltrates, sinusitis, eosinophilia (13.9 cells/ml), myocarditis, arthralgias and myalgias. ANCA serology was negative. Because of EGPA-related heart involvement, corticosteroids and 6 cyclophosphamide pulses were prescribed.

Two months later, he was admitted to the intensive care unit (ICU) with cardiac arrest. ECG showed asystole caused by severe hyperkalemia and renal failure resulting from decompensated corticosteroid-induced diabetes and angiotensin-converting-enzyme–inhibitor treatment. He recovered normal electric activity after cardiopulmonary resuscitation and adrenaline. His condition improved with insulin therapy and volume resuscitation. Azathioprine (150 mg/day) maintenance therapy was started but soon replaced by mycophenolate mofetil (1 g bid) due to toxidermia.

In January 2008, when a β-blocker was introduced, his condition worsened. Cardiac magnetic resonance imaging (CMRI) (Figure 2) revealed severe dilated cardiomyopathy, mitral regurgitation, subepicardial delayed contrast enhancement in the septum and anterior wall, and T2-weighted hyperintensity in the same myocardial territory, consistent with edema. These findings were suggestive of active EGPA-related cardiomyopathy. He underwent OHT in March 2008 at Pitié–Salpêtrière Hospital, Paris, France. Despite numerous post-operative complications (septic mediastinitis, septic shock due to *Enterobacter aerogenes* ventilator-associated pneumonia, acute CMV infection, severe polyneuromyopathy and chronic diarrhea due to *Enterocytozoon bieneusi*), he achieved full neurologic and functional recovery. However, he developed chronic kidney disease (glomerular filtration rate ~40 ml/minute in 2012) as sequelae. Thirteen months post-OHT, EMB showed an acute grade-1R CMR (asymptomatic thus not requiring corticosteroids). Twenty-one months later, an asthma exacerbation required increasing the prednisone dose.

Four years post-OHT, under a regimen of prednisone (10 mg/day), cyclosporine and mycophenolate mofetil, he has experienced no EGPA relapse or other graft rejection in routine EMBs.

Case 3

In 1999, a 36-year-old woman developed late-onset asthma followed, in June 2000, by severe CHF, intracavitary thrombosis, bilateral transudative pleural effusions, skin purpura, sinusitis and eosinophilia (1.9 cells/ml). EGPA was diagnosed in September 2000. ANCA serology was negative. Segmental pulmonary embolism and a right apical nodule were fortuitously diagnosed on her computed-tomography (CT) scan. EMB was uninformative. Despite corticosteroids, anticoagulant and cyclophosphamide pulses, she was transferred to the ICU under dobutamine, high-dose furosemide and interferon-α (3 MIU 3 times a week) added to her regimen. Echocardiography after dobutamine withdrawal estimated her LVEF at 15%. OHT was performed in October 2000 at Pitié–Salpêtrière Hospital.

Under immunosuppressants (tapering doses of prednisone, azathioprine 50 mg bid, cyclosporine 550 mg/day), her weekly EMB showed no sign of acute allograft rejection. In early

February 2001, she developed acute sinusitis and prednisone was increased to 60 mg/day by an ENT specialist. On 12 February 2001, she succumbed to sudden death, complaining of intense abdominal pain. Because no autopsy was performed, we can only speculate on the cause of her death. First, gastrointestinal perforation and subsequent fulminant peritonitis is a plausible explanation. ~~Second, since no human leukocyte antigen (HLA) class-II gene typing was performed and there were 4 donor-recipient HLA class-I mismatches, she was also at high immunologic risk. Thus, acute arrhythmia due to graft rejection is another plausible explanation. Lastly, even though she had received cyclophosphamide pulses prior to OHT and she was currently taking high corticosteroid doses, an EGPA relapse cannot be formally excluded.~~ Second, even though she had received cyclophosphamide pulses prior to OHT and was currently taking high corticosteroid doses, an EGPA relapse cannot be formally excluded. Lastly, graft rejection seems highly unlikely in this setting.

Case 4

In February 2003, a 35-year-old woman with a 15-year history of adult-onset asthma developed fulminant CHF secondary to myocarditis, requiring an intra-aortic balloon pump support (IABP). Initial laboratory analyses revealed marked eosinophilia (9.6 cells/ml). Her chest X-ray showed diffuse perihilar infiltrates suggestive of pulmonary edema and pleural effusions. A week later, a thoracic computed-tomography (CT) scan revealed a left infrahilar nodule. Echocardiography estimated LVEF at 25%. Bronchoscopy was uninformative. The patient initially received medical support and hydrocortisone. Work-up for an infectious or atopic etiology was negative. Transbronchial biopsy of the lung lesion revealed a fibrinopurulent exudate with Charcot–Laden crystals consistent with degenerating eosinophils. Prednisone (70 mg/day) was prescribed and she was discharged.

Thereafter, she was readmitted for a fainting episode attributed to hypotension and referred to another center where EGPA was diagnosed in late June 2003. Azathioprine (50 mg tid) was started, and corticosteroids were tapered and then stopped by November 2003, when a control thoracic CT scan showed resolution of the lung mass. In January 2004, an upper respiratory infection was treated with antibiotics and prednisone (30 mg/day). In March 2004, despite azathioprine, echocardiography

found persistently low LVEF (20%) and a metabolic stress-test measured peak oxygen consumption at 15.8 ml/kg/minute (50% of the predicted value for her age). OHT was performed 2 May 2004 at the Cleveland Clinic, Cleveland, OH, USA. On 10 May, she received corticosteroid pulses for grade-3R CMR.

Six months post-OHT, the patient developed shingles and another upper respiratory infection. Prednisone was withdrawn but restarted in August 2005, when she was taking cyclosporine (100 mg qid) and mycophenolate mofetil (125 mg qid) because of recurrent eosinophilia and asthma exacerbation. Long-term post-OHT medications include cyclosporine (100 mg bid), mycophenolate mofetil (1 g bid), prednisone (4 mg qid), lisinopril (5 mg bid), aciclovir (800 mg bid) and bronchodilatators as needed. Eight years post-OHT, no major EGPA relapse has occurred and no graft rejection has been seen on routine EMBs.

Case 5

In 2004, a 50-year-old patient, with a history of several bronchitis episodes during winters, systemic hypertension and dyslipidemia was diagnosed with EGPA: late-onset asthma, arthralgias, myalgias, skin purpura and subcutaneous nodules, mononeuritis multiplex and blood eosinophilia (9.79 cells/ml). ANCA serology was negative. Corticosteroids were started (initially 1 mg/kg/day for 3 weeks then doses were tapered).

Eighteen months later, in December 2005, while the patient's symptoms regressed under corticosteroids, he was admitted to the ICU for CHF, chest pain and high troponin I levels (> 8 pg/ml). An 18-lead ECG showed no ST-segment abnormality but a grade-1 atrioventricular block. Echocardiography estimated LVEF at 18%, global hypokinesia, dilated left heart chambers, moderate mitral insufficiency and pericardial effusion. Coronary angiogram was normal. Histologic examination of an EMB revealed fibrinoid necrosis, an eosinophil-rich inflammatory infiltrate, extravascular granulomas and MF, thereby confirming the diagnosis of EGPA-related cardiomyopathy. Despite intensive therapy and positive inotropic support, his condition worsened. Emergency OHT was performed in March 2006 in the Sanatorio de la Trinidad Mitre Hospital, Buenos Aires, Argentina.

The patient experienced several post-OHT complications. First, immunosuppressant side effects necessitated switching mycophenolate mofetil to azathioprine because of gastrointestinal disorders and cyclosporine to everolimus in early 2012 to counter moderate kidney failure, then 6 years post-OHT he developed corticosteroid-associated aseptic necrosis of the hip requiring arthroplasty. Second, 2 years post-OHT he developed disseminated miliary tuberculosis (involving lung, peritoneum and skin) that was treated with a 12-months of anti-tuberculosis drugs (including 2 months of quadritherapy); 2 years after the end of treatment, he suffered a skin relapse and is currently taking isoniazid and rifampicin. Third, EGPA relapsed (skin purpura) 48 months post-OHT requiring prednisone intensification. Finally, he was recently diagnosed with severe grade-3 cardiac allograft vasculopathy (CAV) on a routine coronary angiogram. He is currently taking prednisone (40 mg/day), everolimus (1.5 mg/day) and azathioprine (150 mg/day).

Case 6

A 62-year-old man, with a history of late-onset asthma, anaphylactic shock after a bee sting, polypectomy for nasal polyposis, systemic hypertension and ventricular extrasystoles treated since 2007 with carvedilol and flecainide, was admitted to the ICU in March 2008 with CHF and anterior ST-segment elevation. Transthoracic echocardiography estimated LVEF at 25% and visualized anterior hypokinesia, moderate mitral and tricuspid regurgitations, and an apical thrombus. The coronary angiogram was normal and chest CT angiography showed no evidence of pulmonary embolism. Blood analyses revealed hypereosinophilia (12.5 cells/ml). The patient's condition finally improved with positive inotropic support and standard medical therapy. In June 2008, before discharge, an automatic cardioverter defibrillator was implanted because of frequent episodes of unsustained ventricular tachycardia.

In August 2008, he was readmitted for CHF and malignant hypertension unresponsive to dopamine, nitroprusside and diuretics, and he was transferred to the ICU, where adrenaline, milrinone and IABP were started. Blood hypereosinophilia was confirmed. EMB contained an eosinophil-rich inflammatory infiltrate and EGPA was diagnosed. The patient was started on corticosteroids and

underwent “extremely urgent” OHT on 16 September 2008 in Niguarda Ca’ Granda Hospital in Milan, Italy.

The post-operative period was marked by acute CMV pneumonia, extended-spectrum *β*-lactamase *Enterobacter cloacae* sepsis and serum *Aspergillus* galactomannan antigen became positive. He was successfully treated with ganciclovir, imipenem and voriconazole. In January 2009, EMB showed acute grade-1R CMR. Pulse corticosteroids were not administered but cyclosporine maintenance was switched to tacrolimus.

Four years post-OHT, under prednisone (7.5 mg/day), tacrolimus (5 mg/day) and azathioprine (50 mg/day), EMBs scheduled biannually have shown no evidence of graft rejection. The patient is well but has mild functional limitations due to chronic renal dysfunction and osteoporosis.

Case 7

A 35-year-old woman was diagnosed with EGPA in 2003. Part of her medical history was previously reported.[1] A few weeks postpartum, she developed fever, severe asthma, skin petechiae, polyarthralgia and CHF. Blood tests revealed 17.5 eosinophils/ml and a high troponin I level. ANCA serology was negative. EMB-histology findings included an eosinophil-rich inflammatory infiltrate, leukocytoclasia, fibrinoid necrosis and myocardial necrosis. Despite intensive care (mechanical ventilation, inotropes, left ventricular assist device) and corticosteroids, several ventricular arrhythmia episodes (tachycardia and fibrillation) occurred. OHT was performed successfully on 30 March 2003, in San Matteo Hospital, Pavia, Italy. Examination of the explanted heart found the same histopathologic pattern as pre-transplantation EMB. The patient’s health improved, and she was discharged on prednisone, cyclosporine (600 mg/day), statin and a calcium-channel blocker.

She had no clinical or biologic sign of disease activity at her last consultation in September 2008: echocardiography, routine coronarography and EMB were normal. In December 2008, a few days after influenza vaccination, she developed fever, arthralgias and myalgias, and died suddenly. No autopsy was performed. An infectious disease (particularly viral myocarditis) or acute arrhythmia due to EGPA relapse and/or graft rejection are plausible explanations of the patient’s death. Notably, the

patient was at high immunologic risk. Indeed, she had had several pregnancies, had benefited from a left ventricular heart assist device before transplantation and had received 12 units of red blood cells during the procedure. Finally, no HLA typing and no anti-HLA antibody screening had been performed.

Case 8

Part of this case was previously reported.[2] Briefly, a 38-year-old man, with a 1-year history of late-onset asthma treated with inhaled steroids, was hospitalized in October 2004 for dyspnea and chest discomfort. Physical examination found bilateral wheezing and symmetric swelling of both legs consistent with edema. Laboratory findings were elevated C-reactive protein (69.2 mg/liter), troponin I (4.06 μg/liter) and blood eosinophilia (8.5 cells/ml). ECG showed sinus tachycardia, delayed R progression on V1–V4, ST-elevation on V1–V2 and ST depression on V6. LVEF was estimated at 30% by echocardiography, which also revealed a 300-ml pericardial effusion. Chest X-ray showed bilateral lung infiltrates; coronary angiogram was normal. Although immunofluorescence testing for ANCA yielded a cytoplasmic-labeling pattern, enzyme-linked immunosorbent assay was negative for antibodies to proteinase-3 or myeloperoxidase. EMB contained an eosinophil-rich infiltrate and EGPA was diagnosed.

Oral immunosuppressants (prednisone 40 mg/day and methotrexate 15 mg twice weekly) were started. During prednisone tapering, the patient's condition deteriorated with CHF, asthma exacerbation and further LVEF decline, echocardiographically evaluated at 22%. Cyclophosphamide pulses were started to replace methotrexate. Despite simultaneous adjusted heart-failure medication, LVEF declined to 15% in February 2005, when he was placed on the "urgent" heart-transplantation waiting list. OHT was performed in October 2005 in the University of Heidelberg Hospital, Germany. Nine months post-OHT, under corticosteroids, tacrolimus (3 mg/day) and mycophenolate mofetil (1 g bid), routine EMB revealed acute grade-1R CMR that did not require immunosuppressant intensification. To date, that has been the only graft-rejection episode, and no EGPA relapse has occurred. However, in spring 2012, he developed venous occlusion of the retina and macular edema

requiring a slow-release intravitreal dexamethasone implant. Seven years post-OHT, the patient is well and has no activity limitation.

Case 9

This patient's medical history has already been published.[3,4] Briefly, a previously healthy 22-year-old man was diagnosed with pulmonary eosinophilia in July 1986 [breathlessness, wheezing, bilateral interstitial lung opacities and pronounced eosinophilia (7.7 cells/ml). Despite corticosteroids, he developed CHF 1 year later due to severe dilated cardiomyopathy (LVEF estimated at 15%) and recurrent eosinophilia (3 eosinophils/ml). EMB contained prominent foci of young fibroblasts with necrotic and hypertrophied myocytes, and an infiltrate of lymphocytes, plasma cells, and eosinophils. No vasculitis was seen. Despite higher corticosteroid doses, he developed cardiogenic shock that required adrenaline, IABP and mechanical ventilation. OHT was performed in October 1987 in the Wythenshawe Hospital, Manchester, UK. Histologic examination of the explanted heart revealed foci of fibrinoid necrosis with giant cells in some intramyocardial vessels, mild eosinophilic infiltrate, subendocardial necrosis and arteritis in the right coronary artery. EGPA-related cardiomyopathy was diagnosed.

Two months after discharge, and despite immunosuppressants (i.e. corticosteroids and antithymoglobulins as induction therapy, and cyclosporine and azathioprine maintenance), the patient's EGPA relapsed [cough, breathlessness and recurrent eosinophilia (2 eosinophils/ml], without any EMB sign of acute CMR, and corticosteroid dose was increased. Routine EMB showed no rejection or vasculitis until March 1991, when a moderate myocardial rejection episode was treated with a higher corticosteroid dose. In March 1992, he collapsed suddenly and died shortly thereafter, despite immediate cardiopulmonary resuscitation. Postmortem examination of the transplanted heart showed patchy areas of heart rejection and diffuse fibrinoid necrosis, chronic inflammation (containing lymphocytes, plasma cells and a few eosinophils) and proximal thrombotic occlusion of the right coronary artery, suggestive of an EGPA relapse.

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SUPPLEMENTAL TABLES

Table S1 The 2004 International Society of Heart and Lung Transplantation Cardiac Biopsy Grading for Acute Cellular Rejection[aS]

Grade	Definition
0R	No rejection
1R, mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage
2R, moderate	Two or more foci of infiltrate with associated myocyte damage
3R, severe	Diffuse infiltrate with multifocal myocyte damage with or without edema, hemorrhage, or vasculitis

[a]Modified after Stewart et al. J Heart Lung Transplant 2005;24:1710-20.

Table S2 The 2011 International Society of Heart and Lung Transplantation Working Formulation for Pathologic Diagnosis of Antibody-Mediated Rejection (pAMR)[a]

pAMR	Description
0	Histologic and immunopathologic studies are negative
1 (H^{+})	Positive histologic findings and negative immunopathologic findings
1 (I^{+})	Negative histologic findings and positive immunopathologic findings
2	Histologic and immunopathologic findings are present
3	Severe AMR with histopathologic findings of interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis and/or karyorrhexis and marked edema

[a]Modified after Berry et al. J Heart Lung Transplant 2011;24:1710-20.

ABBREVIATIONS

AMR, antibody-mediated rejection; ANCA, antineutrophil cytoplasm antibodies; CAV, cardiac allograft vasculopathy; CHF, congestive heart failure; CMRI, cardiac magnetic resonance imaging; CMR, cell-mediated rejection; CMV, cytomegalovirus; CT, computed tomography; EGPA, eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); EMB, endomyocardial biopsy; ENT = ear, nose and throat; IABP, intra-aortic balloon pump; HLA, human lymphocyte antigen; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MF, myocardial fibrosis; OHT, orthotopic heart transplantation.

CASE REPORTS

Case 1

A woman born in 1955 was diagnosed with eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) (EGPA) in 1985 based on asthma, differential white-blood-cell–count eosinophilia, non-fixed pulmonary infiltrates, chronic paranasal sinus pain, skin biopsy showing perivascular inflammation with dense eosinophilic infiltrate and giant-cell granuloma in a context of arthralgias and pericarditis. Antineutrophil cytoplasm antibody (ANCA) serology was negative. Various treatments including azathioprine, methotrexate, cyclosporine and mycophenolate mofetil were administered until 2009. During those years, she had many relapses, and successively developed polyneuritis, retro-tympanic granuloma and eosinophilic gastroenteritis, while control of her asthma required continuous corticosteroids.

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an eosinophil-rich infiltrate (Figure 2). Outcome was favorable with immunosuppressive therapy (cyclosporine 175 mg bid, and azathioprine 75 mg/day enabling prednisone tapering), cardioactive therapy (atenolol 25 mg/day, ramipril 2.5 mg/day, aspirin 100 mg/day, and simavastatin 20 mg/day) and anti-cytomegalovirus (CMV) prophylaxis (valganciclovir 450 mg/day).

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In July 2011, despite the absence of clinical or biologic signs of EGPA activity, the patient died suddenly. No autopsy was performed.

Case 2

In July 2007, a 52-year-old man, with a 3-year history of asthma and a CHF episode with normal coronary angiogram 3 years earlier, was diagnosed with EGPA: late asthma, non-fixed pulmonary infiltrates, sinusitis, eosinophilia (13.9 cells/ml), myocarditis, arthralgias and myalgias. ANCA serology was negative. Because of EGPA-related heart involvement, corticosteroids and 6 cyclophosphamide pulses were prescribed.

Two months later, he was admitted to the intensive care unit (ICU) with cardiac arrest. ECG showed asystole caused by severe hyperkalemia and renal failure resulting from decompensated corticosteroid-induced diabetes and angiotensin-converting-enzyme–inhibitor treatment. He recovered normal electric activity after cardiopulmonary resuscitation and adrenaline. His condition improved with insulin therapy and volume resuscitation. Azathioprine (150 mg/day) maintenance therapy was started but soon replaced by mycophenolate mofetil (1 g bid) due to toxidermia.

In January 2008, when a β-blocker was introduced, his condition worsened. Cardiac magnetic resonance imaging (CMRI) (Figure 2) revealed severe dilated cardiomyopathy, mitral regurgitation, subepicardial delayed contrast enhancement in the septum and anterior wall, and T2-weighted hyperintensity in the same myocardial territory, consistent with edema. These findings were suggestive of active EGPA-related cardiomyopathy. He underwent OHT in March 2008 at Pitié–Salpêtrière Hospital, Paris, France. Despite numerous post-operative complications (septic mediastinitis, septic shock due to *Enterobacter aerogenes* ventilator-associated pneumonia, acute CMV infection, severe polyneuromyopathy and chronic diarrhea due to *Enterocytozoon bieneusi*), he achieved full neurologic and functional recovery. However, he developed chronic kidney disease (glomerular filtration rate ~40 ml/minute in 2012) as sequelae. Thirteen months post-OHT, EMB showed an acute grade-1R CMR (asymptomatic thus not requiring corticosteroids). Twenty-one months later, an asthma exacerbation required increasing the prednisone dose.

Four years post-OHT, under a regimen of prednisone (10 mg/day), cyclosporine and mycophenolate mofetil, he has experienced no EGPA relapse or other graft rejection in routine EMBs.

Case 3

In 1999, a 36-year-old woman developed late-onset asthma followed, in June 2000, by severe CHF, intracavitary thrombosis, bilateral transudative pleural effusions, skin purpura, sinusitis and eosinophilia (1.9 cells/ml). EGPA was diagnosed in September 2000. ANCA serology was negative. Segmental pulmonary embolism and a right apical nodule were fortuitously diagnosed on her computed-tomography (CT) scan. EMB was uninformative. Despite corticosteroids, anticoagulant and cyclophosphamide pulses, she was transferred to the ICU under dobutamine, high-dose furosemide and interferon-α (3 MIU 3 times a week) added to her regimen. Echocardiography after dobutamine withdrawal estimated her LVEF at 15%. OHT was performed in October 2000 at Pitié–Salpêtrière Hospital.

Under immunosuppressants (tapering doses of prednisone, azathioprine 50 mg bid, cyclosporine 550 mg/day), her weekly EMB showed no sign of acute allograft rejection. In early

February 2001, she developed acute sinusitis and prednisone was increased to 60 mg/day by an ENT specialist. On 12 February 2001, she succumbed to sudden death, complaining of intense abdominal pain. Because no autopsy was performed, we can only speculate on the cause of her death. First, gastrointestinal perforation and subsequent fulminant peritonitis is a plausible explanation. Second, even though she had received cyclophosphamide pulses prior to OHT and was currently taking high corticosteroid doses, an EGPA relapse cannot be formally excluded. Lastly, graft rejection seems highly unlikely in this setting.

Case 4

In February 2003, a 35-year-old woman with a 15-year history of adult-onset asthma developed fulminant CHF secondary to myocarditis, requiring an intra-aortic balloon pump support (IABP). Initial laboratory analyses revealed marked eosinophilia (9.6 cells/ml). Her chest X-ray showed diffuse perihilar infiltrates suggestive of pulmonary edema and pleural effusions. A week later, a thoracic computed-tomography (CT) scan revealed a left infrahilar nodule. Echocardiography estimated LVEF at 25%. Bronchoscopy was uninformative. The patient initially received medical support and hydrocortisone. Work-up for an infectious or atopic etiology was negative. Transbronchial biopsy of the lung lesion revealed a fibrinopurulent exudate with Charcot–Laden crystals consistent with degenerating eosinophils. Prednisone (70 mg/day) was prescribed and she was discharged.

Thereafter, she was readmitted for a fainting episode attributed to hypotension and referred to another center where EGPA was diagnosed in late June 2003. Azathioprine (50 mg tid) was started, and corticosteroids were tapered and then stopped by November 2003, when a control thoracic CT scan showed resolution of the lung mass. In January 2004, an upper respiratory infection was treated with antibiotics and prednisone (30 mg/day). In March 2004, despite azathioprine, echocardiography found persistently low LVEF (20%) and a metabolic stress-test measured peak oxygen consumption at 15.8 ml/kg/minute (50% of the predicted value for her age). OHT was performed 2 May 2004 at the Cleveland Clinic, Cleveland, OH, USA. On 10 May, she received corticosteroid pulses for grade-3R CMR.

Six months post-OHT, the patient developed shingles and another upper respiratory infection. Prednisone was withdrawn but restarted in August 2005, when she was taking cyclosporine (100 mg qid) and mycophenolate mofetil (125 mg qid) because of recurrent eosinophilia and asthma exacerbation. Long-term post-OHT medications include cyclosporine (100 mg bid), mycophenolate mofetil (1 g bid), prednisone (4 mg qid), lisinopril (5 mg bid), aciclovir (800 mg bid) and bronchodilatators as needed. Eight years post-OHT, no major EGPA relapse has occurred and no graft rejection has been seen on routine EMBs.

Case 5

In 2004, a 50-year-old patient, with a history of several bronchitis episodes during winters, systemic hypertension and dyslipidemia was diagnosed with EGPA: late-onset asthma, arthralgias, myalgias, skin purpura and subcutaneous nodules, mononeuritis multiplex and blood eosinophilia (9.79 cells/ml). ANCA serology was negative. Corticosteroids were started (initially 1 mg/kg/day for 3 weeks then doses were tapered).

Eighteen months later, in December 2005, while the patient's symptoms regressed under corticosteroids, he was admitted to the ICU for CHF, chest pain and high troponin I levels (> 8 pg/ml). An 18-lead ECG showed no ST-segment abnormality but a grade-1 atrioventricular block. Echocardiography estimated LVEF at 18%, global hypokinesia, dilated left heart chambers, moderate mitral insufficiency and pericardial effusion. Coronary angiogram was normal. Histologic examination of an EMB revealed fibrinoid necrosis, an eosinophil-rich inflammatory infiltrate, extravascular granulomas and MF, thereby confirming the diagnosis of EGPA-related cardiomyopathy. Despite intensive therapy and positive inotropic support, his condition worsened. Emergency OHT was performed in March 2006 in the Sanatorio de la Trinidad Mitre Hospital, Buenos Aires, Argentina.

The patient experienced several post-OHT complications. First, immunosuppressant side effects necessitated switching mycophenolate mofetil to azathioprine because of gastrointestinal disorders and cyclosporine to everolimus in early 2012 to counter moderate kidney failure, then 6 years post-OHT he developed corticosteroid-associated aseptic necrosis of the hip requiring

arthroplasty. Second, 2 years post-OHT he developed disseminated miliary tuberculosis (involving lung, peritoneum and skin) that was treated with a 12-months of anti-tuberculosis drugs (including 2 months of quadritherapy); 2 years after the end of treatment, he suffered a skin relapse and is currently taking isoniazid and rifampicin. Third, EGPA relapsed (skin purpura) 48 months post-OHT requiring prednisone intensification. Finally, he was recently diagnosed with severe grade-3 cardiac allograft vasculopathy (CAV) on a routine coronary angiogram. He is currently taking prednisone (40 mg/day), everolimus (1.5 mg/day) and azathioprine (150 mg/day).

Case 6

A 62-year-old man, with a history of late-onset asthma, anaphylactic shock after a bee sting, polypectomy for nasal polyposis, systemic hypertension and ventricular extrasystoles treated since 2007 with carvedilol and flecainide, was admitted to the ICU in March 2008 with CHF and anterior ST-segment elevation. Transthoracic echocardiography estimated LVEF at 25% and visualized anterior hypokinesia, moderate mitral and tricuspid regurgitations, and an apical thrombus. The coronary angiogram was normal and chest CT angiography showed no evidence of pulmonary embolism. Blood analyses revealed hypereosinophilia (12.5 cells/ml). The patient's condition finally improved with positive inotropic support and standard medical therapy. In June 2008, before discharge, an automatic cardioverter defibrillator was implanted because of frequent episodes of unsustained ventricular tachycardia.

In August 2008, he was readmitted for CHF and malignant hypertension unresponsive to dopamine, nitroprusside and diuretics, and he was transferred to the ICU, where adrenaline, milrinone and IABP were started. Blood hypereosinophilia was confirmed. EMB contained an eosinophil-rich inflammatory infiltrate and EGPA was diagnosed. The patient was started on corticosteroids and underwent "extremely urgent" OHT on 16 September 2008 in Niguarda Ca' Granda Hospital in Milan, Italy.

The post-operative period was marked by acute CMV pneumonia, extended-spectrum β-lactamase *Enterobacter cloacae* sepsis and serum *Aspergillus* galactomannan antigen became positive.

He was successfully treated with ganciclovir, imipenem and voriconazole. In January 2009, EMB showed acute grade-1R CMR. Pulse corticosteroids were not administered but cyclosporine maintenance was switched to tacrolimus.

Four years post-OHT, under prednisone (7.5 mg/day), tacrolimus (5 mg/day) and azathioprine (50 mg/day), EMBs scheduled biannually have shown no evidence of graft rejection. The patient is well but has mild functional limitations due to chronic renal dysfunction and osteoporosis.

Case 7

A 35-year-old woman was diagnosed with EGPA in 2003. Part of her medical history was previously reported.[1] A few weeks postpartum, she developed fever, severe asthma, skin petechiae, polyarthralgia and CHF. Blood tests revealed 17.5 eosinophils/ml and a high troponin I level. ANCA serology was negative. EMB-histology findings included an eosinophil-rich inflammatory infiltrate, leukocytoclasia, fibrinoid necrosis and myocardial necrosis. Despite intensive care (mechanical ventilation, inotropes, left ventricular assist device) and corticosteroids, several ventricular arrhythmia episodes (tachycardia and fibrillation) occurred. OHT was performed successfully on 30 March 2003, in San Matteo Hospital, Pavia, Italy. Examination of the explanted heart found the same histopathologic pattern as pre-transplantation EMB. The patient's health improved, and she was discharged on prednisone, cyclosporine (600 mg/day), statin and a calcium-channel blocker.

She had no clinical or biologic sign of disease activity at her last consultation in September 2008: echocardiography, routine coronarography and EMB were normal. In December 2008, a few days after influenza vaccination, she developed fever, arthralgias and myalgias, and died suddenly. No autopsy was performed. An infectious disease (particularly viral myocarditis) or acute arrhythmia due to EGPA relapse and/or graft rejection are plausible explanations of the patient's death. Notably, the patient was at high immunologic risk. Indeed, she had had several pregnancies, had benefited from a left ventricular heart assist device before transplantation and had received 12 units of red blood cells during the procedure. Finally, no HLA typing and no anti-HLA antibody screening had been performed.

Case 8

Part of this case was previously reported.[2] Briefly, a 38-year-old man, with a 1-year history of late-onset asthma treated with inhaled steroids, was hospitalized in October 2004 for dyspnea and chest discomfort. Physical examination found bilateral wheezing and symmetric swelling of both legs consistent with edema. Laboratory findings were elevated C-reactive protein (69.2 mg/liter), troponin I (4.06 μg/liter) and blood eosinophilia (8.5 cells/ml). ECG showed sinus tachycardia, delayed R progression on V1–V4, ST-elevation on V1–V2 and ST depression on V6. LVEF was estimated at 30% by echocardiography, which also revealed a 300-ml pericardial effusion. Chest X-ray showed bilateral lung infiltrates; coronary angiogram was normal. Although immunofluorescence testing for ANCA yielded a cytoplasmic-labeling pattern, enzyme-linked immunosorbent assay was negative for antibodies to proteinase-3 or myeloperoxidase. EMB contained an eosinophil-rich infiltrate and EGPA was diagnosed.

Oral immunosuppressants (prednisone 40 mg/day and methotrexate 15 mg twice weekly) were started. During prednisone tapering, the patient's condition deteriorated with CHF, asthma exacerbation and further LVEF decline, echocardiographically evaluated at 22%. Cyclophosphamide pulses were started to replace methotrexate. Despite simultaneous adjusted heart-failure medication, LVEF declined to 15% in February 2005, when he was placed on the "urgent" heart-transplantation waiting list. OHT was performed in October 2005 in the University of Heidelberg Hospital, Germany. Nine months post-OHT, under corticosteroids, tacrolimus (3 mg/day) and mycophenolate mofetil (1 g bid), routine EMB revealed acute grade-1R CMR that did not require immunosuppressant intensification. To date, that has been the only graft-rejection episode, and no EGPA relapse has occurred. However, in spring 2012, he developed venous occlusion of the retina and macular edema requiring a slow-release intravitreal dexamethasone implant. Seven years post-OHT, the patient is well and has no activity limitation.

Case 9

This patient's medical history has already been published.[3,4] Briefly, a previously healthy 22-year-old man was diagnosed with pulmonary eosinophilia in July 1986 [breathlessness, wheezing, bilateral interstitial lung opacities and pronounced eosinophilia (7.7 cells/ml). Despite corticosteroids, he developed CHF 1 year later due to severe dilated cardiomyopathy (LVEF estimated at 15%) and recurrent eosinophilia (3 eosinophils/ml). EMB contained prominent foci of young fibroblasts with necrotic and hypertrophied myocytes, and an infiltrate of lymphocytes, plasma cells, and eosinophils. No vasculitis was seen. Despite higher corticosteroid doses, he developed cardiogenic shock that required adrenaline, IABP and mechanical ventilation. OHT was performed in October 1987 in the Wythenshawe Hospital, Manchester, UK. Histologic examination of the explanted heart revealed foci of fibrinoid necrosis with giant cells in some intramyocardial vessels, mild eosinophilic infiltrate, subendocardial necrosis and arteritis in the right coronary artery. EGPA-related cardiomyopathy was diagnosed.

Two months after discharge, and despite immunosuppressants (i.e. corticosteroids and antithymoglobulins as induction therapy, and cyclosporine and azathioprine maintenance), the patient's EGPA relapsed [cough, breathlessness and recurrent eosinophilia (2 eosinophils/ml], without any EMB sign of acute CMR, and corticosteroid dose was increased. Routine EMB showed no rejection or vasculitis until March 1991, when a moderate myocardial rejection episode was treated with a higher corticosteroid dose. In March 1992, he collapsed suddenly and died shortly thereafter, despite immediate cardiopulmonary resuscitation. Postmortem examination of the transplanted heart showed patchy areas of heart rejection and diffuse fibrinoid necrosis, chronic inflammation (containing lymphocytes, plasma cells and a few eosinophils) and proximal thrombotic occlusion of the right coronary artery, suggestive of an EGPA relapse.

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Table 1 Patient Characteristics at Diagnosis of Eosinophilic Granulomatosis with Polyangiitis

Patient	Year of diagnosis	Sex /age (year)	Clinical manifestations	Eosinophils (/ml)	BVAS
1	1985	F/26	Fever, sinusitis, asthma, lung infiltrates, myalgias, arthralgias, skin nodules, pericarditis	3.2	23
2	2007	M/54	Fever, sinusitis, asthma, lung nodule, lung infiltrates, myalgias, arthralgias, CHF	13.9	31
3	2000	F/36	Fever, sinusitis, asthma, lung nodule, pleural effusion, myalgias, arthralgias, skin purpura, deep vein thrombosis	1.9	4
4	2003	F/35	Sinusitis, asthma, lung nodule, lung infiltrates, pleural effusion, myalgias, arthralgias, hematuria, CHF	9.6	42
5	2004	M/50	Asthma, myalgias, arthralgias, mononeuritis multiplex, skin purpura, skin nodules	9.8	27
6	2008	M/62	Sinusitis, asthma, lung infiltrates, CHF	12.5	22

7	2003	F/35	Fever, sinusitis, asthma, arthralgias, skin purpura, CHF	17.5	38
8	2004	M/38	Fever, sinusitis, asthma, lung infiltrates, pleural effusion, CHF	8.5	42
9	1986	M/22	Fever, asthma, lung infiltrates	7.7	12

ANCA, antineutrophil cytoplasm antibodies; BVAS, Birmingham Vasculitis Activity Score; CHF, congestive heart failure.

Table 2 Patient Characteristics at Diagnosis of EGPA-Related Cardiomyopathy

Patient	EGPA-to-CMP interval (mo)	CV risk factors	Troponin I (μg/liter)	NT pro-BNP (pg/ml)	ECG	LVEF (%)	CMRI	Coronary angiogram	CMP-to-OHT interval (mo)
1	288	High CH	<0.04	3841	ST	33	ND	Normal	7
2	0	Age, smoker	10	1363	AR, ST	30	Anteroseptal STIR hyperintensity & Gd-DE	40% stenosis of the anterior IVA	9
3	12	None	57	ND	AR	19	ND	Normal	15
4	0	High CH	2.8	601	AR, ST	20	ND	ND	15
5	18	Age, HT	8.9	ND	AVB	18	ND	Normal	12
6	0	Age, HT, high CH, FH	ND	16,730	ST	25	ND	Normal	5

7	0	Smoker	20	ND	AR	25	ND	ND	4
8	0	None	4.1	32,397	AR, ST	30	Anterior Gd-DE	Normal	12
9	12	NR	ND	ND	Low voltage	15	ND	ND	2

AR, arrhythmia; AVB, atrioventricular block; CH, cholesterol; CMP, cardiomyopathy; CMRI, cardiac magnetic resonance imaging; CV, cardiovascular; ECG, electrocardiogram; EGPA, eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); FH, family history of CV disease; Gd-DE, gadolinium delayed enhancement; HT, hypertension; IVA, interventricular artery; LVEF, left ventricular ejection fraction; mo, month; ND, not done; NR, not reported; NT pro-BNP, N-terminal prohormone of brain natriuretic peptide; STIR, T2-weighted short axis inversion recovery; ST, ST-segment abnormality.

Table 4

Table 4 Post-Transplantation Outcomes

Patient	OHT year	Treatment			Status	EGPA relapse (mo)	Graft rejection[a] (mo)	CAV	Infection	Other complications	VDI	Follow-up (mo)
		Induction	Maintenance	Cardioactive								
1	2009	ATG	CS, CyA, AZA, MMF, MTX, IVIg	BB, ACEI, statins, AP, D	Died	Yes (5)	CMR 1R, pAMR2 (5)	No	CMV replication	Yes	1	11
2	2008	ATG	CT, CyA, AZA, MMF	ACEI, statins, AP, D	Alive	Asthma flare (34)	CMR 1R (13)	No	Septic mediastinitis, VAP, *Microsporidia*, CMV replication	Yes	9	55
3	2000	OKT3	CS, CyA,	ACEI, statins,	Died	Sinusitis	No	No	None	None	2	3

			AZA	AP		(3)						
4	2004	None	CS, CyA, MMF	BB, ACEI, statins, D	Alive	Asthma flare (15)	CMR 3R (1)	No	Herpes zoster	None	0	102
5	2006	Anti-IL-2R	CS, CyA, PSI, MMF, AZA	ACEI, statins, AP	Alive	Yes (48)	No	Yes	Disseminated tuberculosis	Yes	7	80
6	2008	ATG	CS, CyA, TAC, AZA	ACEI, AP	Alive	No	CMR 1R (4)	No	CMV and *Aspergillus sp.*	Yes	4	47
7	2003	ATG	CS, CyA, AZA	ACEI, statins	Died	No	No	No	None	Yes	0	60
8	2005	None	CS, TAC, MMF	ACEI, statins	Alive	No	CMR 1R (72)	No	None	Yes	3	85
9	1987	ATG	CS, CyA,	NR	Died	Yes (2)	CMR 2R	Yes	CMV	None	ND	53

AZA		(41)	replication

ACEI, angiotensin-converting–enzyme inhibitor or sartan; AMR, antibody-mediated rejection; anti-IL-2R, anti-interleukin-2–receptor antibodies; AP, anti-platelet; ATG, antithymoglobulin; AZA, azathioprine; BB, β-blocker, CAV, cardiac allograft vasculopathy; CH, cholesterol; CMR, cell-mediated rejection; CMV, cytomegalovirus; CS, corticosteroids; CyA, cyclosporine, D, diuretics; DM, diabetes mellitus; EGPA, eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); HT, hypertension; IVIg, intravenous immunoglobulins; MMF, mycophenolate mofetil; MTX, methotrexate; NR, not reported; OHT, orthotopic heart transplantation; OKT3, muromonab-CD3; PSI, proliferation signal inhibitor; TAC, tacrolimus; VAP, ventilator-associated pneumonia; VDI, Vasculitis Damage Index.

[a]See Online Supplemental Material for explanations of grading of biopsies showing acute CMR and AMR working formulation.

Figure 1A

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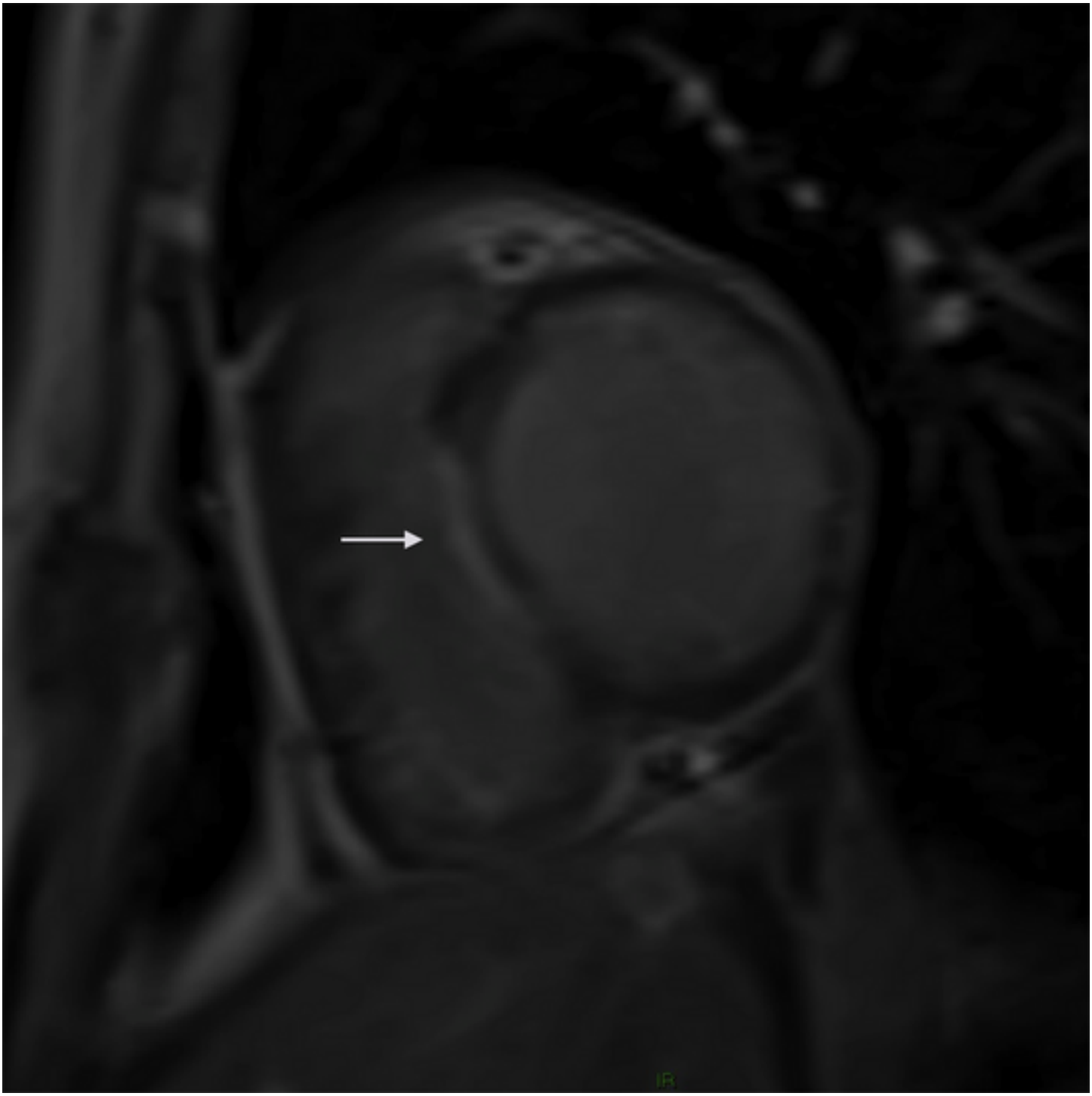

Figure 1B

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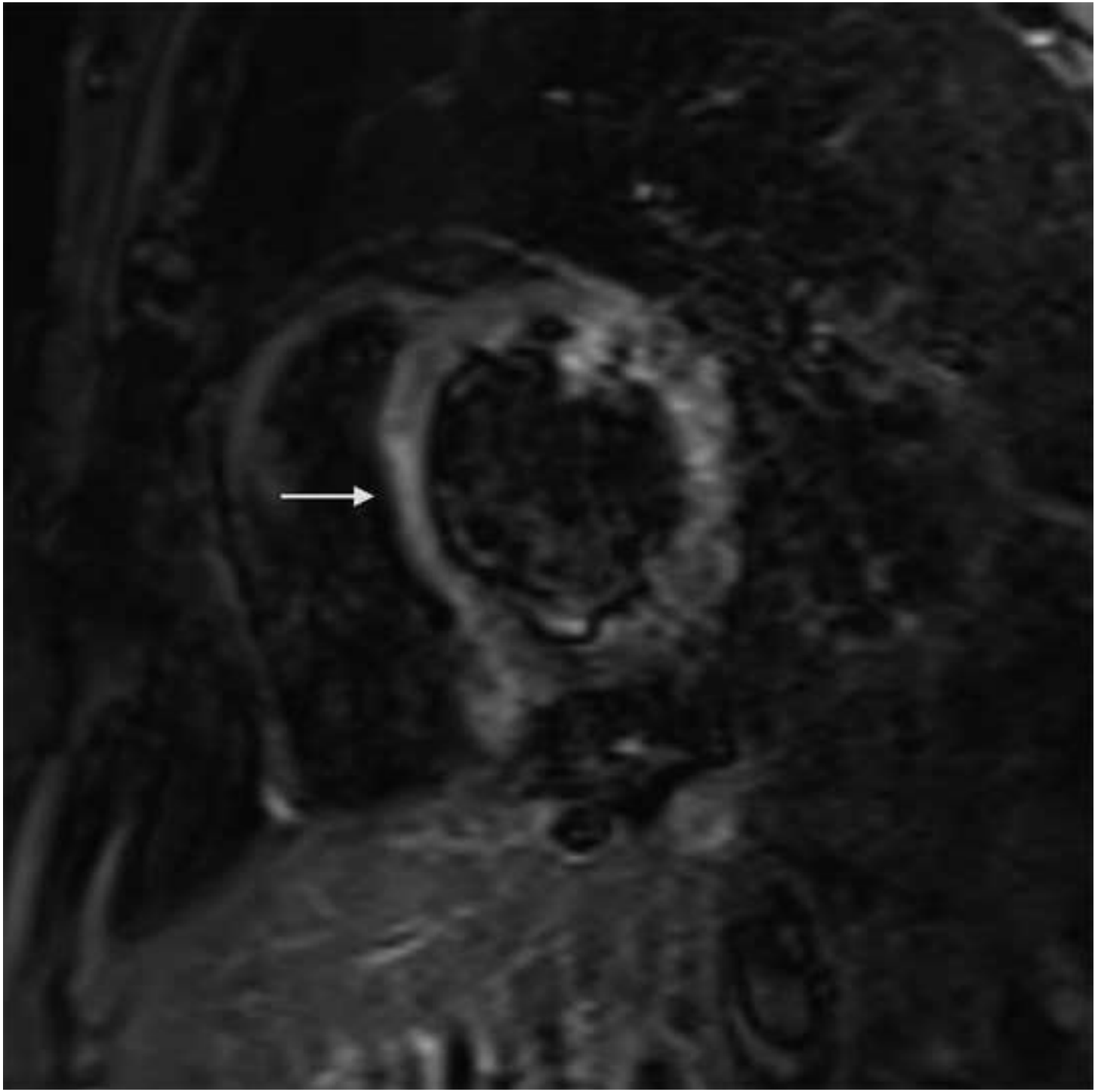

Figure 2A

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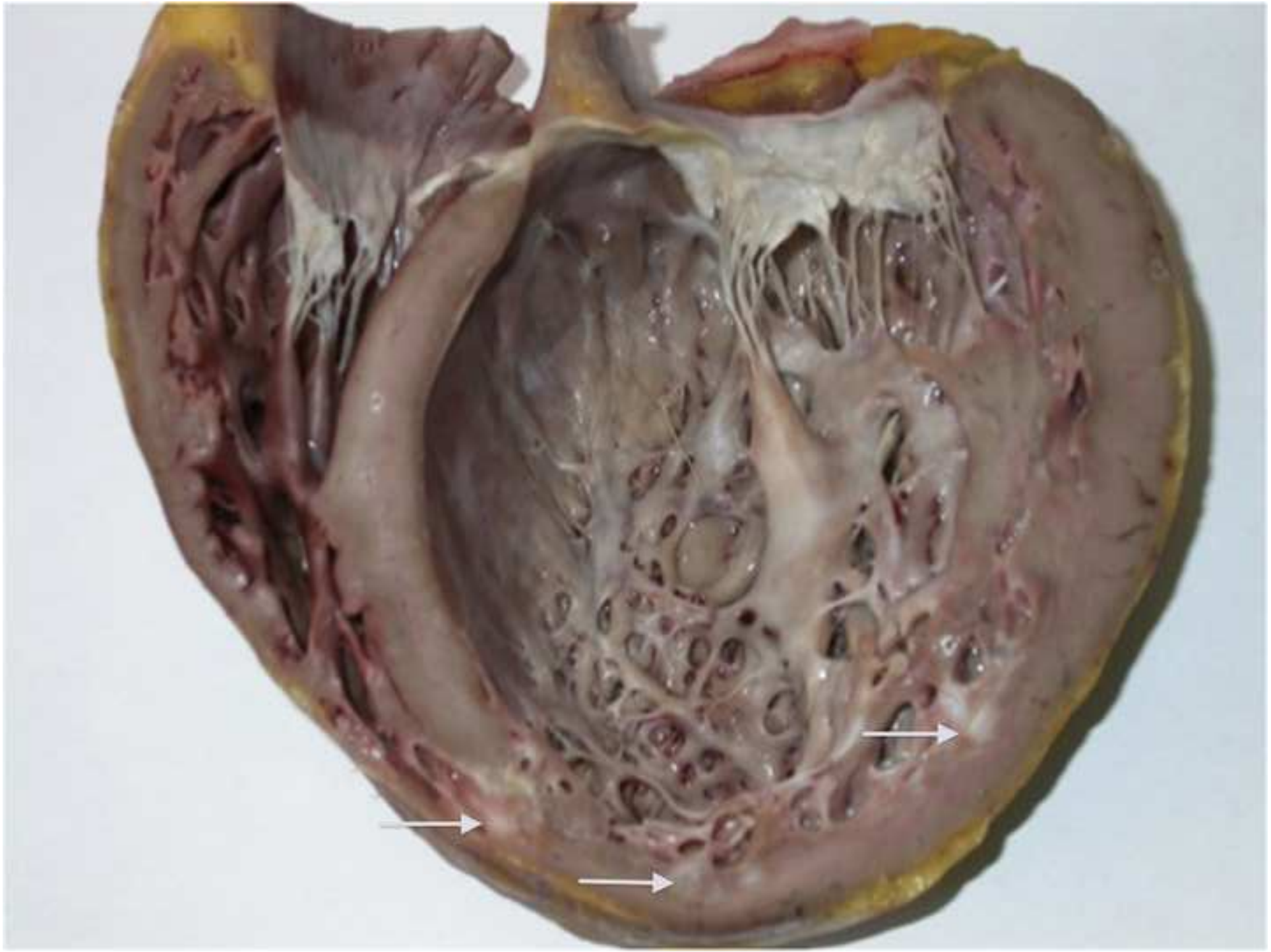

Figure 2B (modified)

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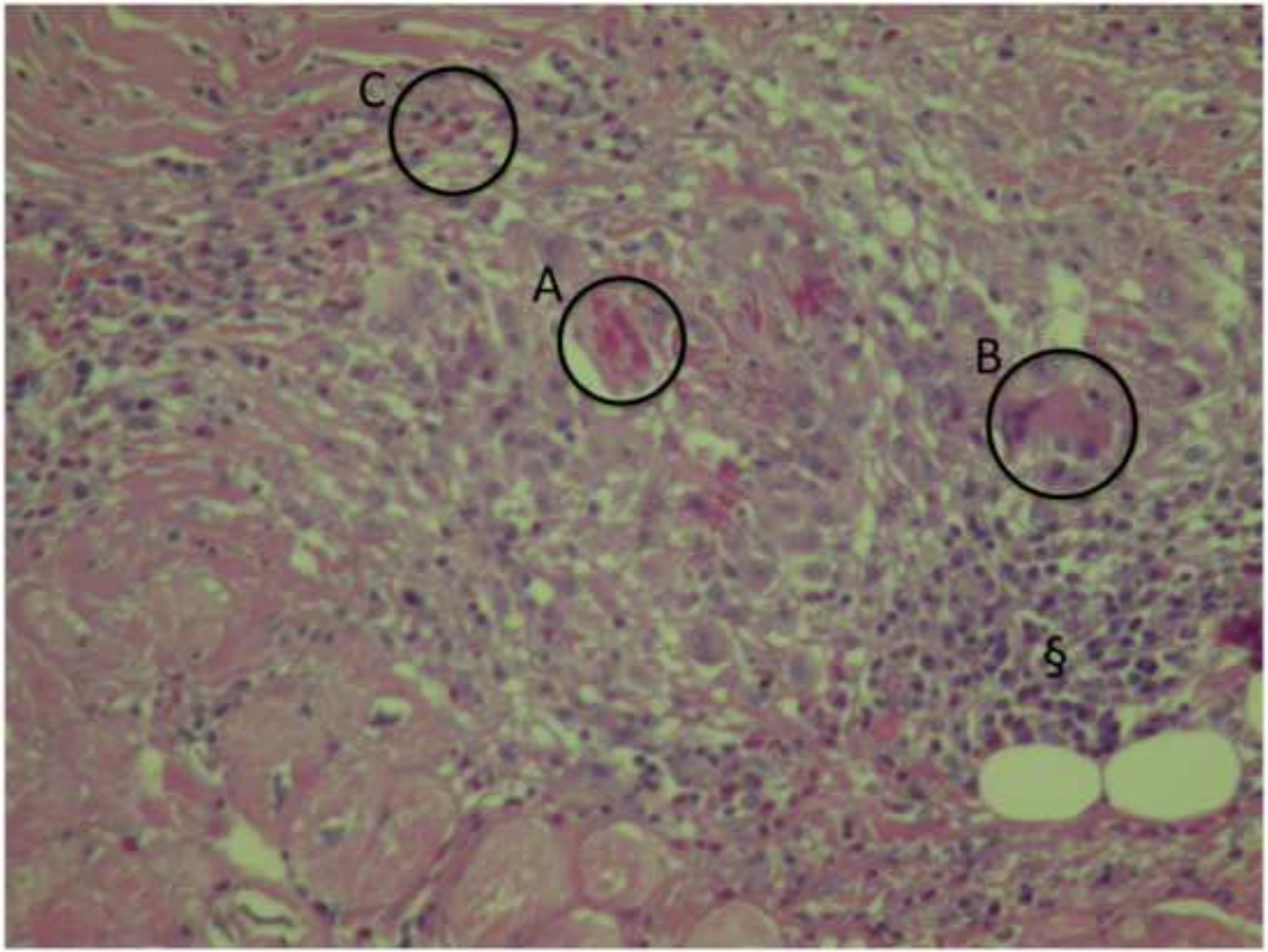

Table 3 Histologic Findings

Patient	Pre-graft EMB	Explanted heart	Post-graft EMB
1	ND	Fibrinoid necrosis, eosinophil-rich inflammatory infiltrate, giant cells, myocardial fibrosis	CMR (1R), AMR (pAMR2), eosinophil-rich inflammatory infiltrate
2	ND	Atheroma, myocardial fibrosis, left ventricular endomyocardial fibrosis	CMR (1R)
3	Normal	Myocardial fibrosis, myocardial necrosis	Normal
4	NR	Small-vessel mixed neutrophilic and lymphocytic infiltrates	CMR (3R)
5	Fibrinoid necrosis, eosinophil-rich inflammatory infiltrate, extravascular granulomas, myocardial fibrosis, myocardial necrosis	Atheroma, fibrinoid necrosis, eosinophil-rich inflammatory infiltrate, myocardial fibrosis, myocardial necrosis	Myocardial necrosis
6	Eosinophil-rich inflammatory infiltrate	Extravascular granulomas, myocardial fibrosis	CMR (1R)
7	Fibrinoid necrosis, leukocytoclasia, eosinophil-	Fibrinoid necrosis, perivascular eosinophil-rich inflammatory	Normal

	rich inflammatory infiltrate, myocardial necrosis	infiltrate, myocardial necrosis, medium-sized coronary branch thromboses	
8	Eosinophil-rich inflammatory infiltrate, myocardial necrosis	Leukocytoclasia, myocardial fibrosis	CMR (1R)
9	Eosinophil-rich inflammatory infiltrate, myocardial necrosis	Fibrinoid necrosis, eosinophil-rich inflammatory infiltrate, myocardial necrosis, giant cells, right coronary artery arteritis	CMR (2R)

AMR, antibody-mediated rejection; pAMR, pathologic AMR; CMR, cell-mediated rejection; EMB, endomyocardial biopsy; ND, not done; NR, not reported.