Pericarditis in Patients With Chronic Graft-vs-Host Disease

E. Karakulska-Prystupiuk*, G. Basak, J. Dwilewicz-Trojaczek, M. Paluszewska, P. Boguradzki, and W. Jędrzejczak

Department of Hematology, Oncology, and Internal Diseases, Medical University of Warsaw, Warsaw, Poland

ABSTRACT

Background. There are only a few cases of pericarditis complications following allogeneic bone marrow transplantation described in the literature and there are no data available on the risk and frequency of this condition. The aim of this study was to assess the frequency of exudative pericarditis complicating chronic graft-vs-host disease in allogeneic hematopoietic cell transplant recipients.

Methods. Retrospective analysis involved a group of 105 patients of the Outpatient Transplantation Service of the Department of Hematology, Medical University of Warsaw, who received transplants in the years 2010–2016 and were evaluated for the years 2014–2016. In this group, 50 patients suffered from chronic graft-vs-host disease (cGVHD), including 24 with moderate or severe disease. Cardiology parameters evaluated included electrocardiography, echocardiography, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and systematic clinical follow-up.

Results. Pericarditis was diagnosed in 6 patients (aged 20–56 years) within 4 to 23 months after allogenic hematopoietic stem cell transplantation. All patients suffered from severe cGVHD with involvement of at least 2 organs but none had earlier history of heart disease. All patients had elevated NT-proBNP and demonstrated signs of heart insufficiency grade II or III according to the New York Heart Association. There were no major changes in electrocardiogram. Only 1 patient improved following glucocorticosteroids as monotherapy, while others required complex approaches including tacrolimus plus sirolimus, rituximab, and extracorporeal photopheresis.

Conclusion. Late pericarditis may occur in up to 5% of allogenic hematopoietic stem cell transplantation survivors, primarily affecting patients with moderate and severe grade cGVHD. It requires escalation of immunosuppressive treatment but usually has favorable outcome. Early diagnosis may be achieved by systematic NT-proBNP testing and periodic echocardiograph evaluation.

ACCORDING to the European Society of Cardiology Guidelines for the diagnosis and management of pericardial diseases, pericardial involvement in systemic autoimmune diseases may be symptomatic (pericarditis or symptomatic pericardial effusion [PE]) and asymptomatic [1]. The pericardium may be affected by all categories of disease including infectious, autoimmune, neoplastic, iatrogenic, and metabolic, but all these causes can overlap after allogeneic hematopoietic stem cell transplantation (HSCT). According to the National Institutes of Health guidelines, PE is considered to be a manifestation of chronic graft-vs-host disease (cGVHD). In the hematopoietic cell transplant setting, this complication is a diagnosis of exclusion [2]. It is seen as an other manifestation in patients with established cGVHD. Its pathophysiology is poorly understood.

*Address correspondence to Ewa Karakulska-Prystupiuk, Medical University of Warsaw, Banacha 1a, 02-097 Warsaw, Poland. Tel: +48 22 599 28 98, Fax: +48 22 599 14 18. E-mail: emkp1234@gmail.com

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Currently there are no published data systematically describing the incidence, clinical characteristics, and outcome of PE in adult stem cell recipients [3]. Also, the response to therapy and long-term outcomes of this cGVHD manifestation have not been well described. All medical therapies for pericardial diseases are off label; no drug has been registered until now for a specific pericardial indication [1].

The aim of this study was to assess the frequency and risk factors of exudative pericarditis complicating cGVHD in allogeneic hematopoietic cell transplant recipients.

MATERIAL AND METHODS

Retrospective analysis involved a group of 105 patients: 38 patients who received transplants from HLA-identical siblings and 67 who received transplants from matched unrelated donors. Seventy-eight patients received myeloablative conditioning and 27 received reduced intensity conditioning.

In this group, 50 patients suffered from cGVHD, including 24 with moderate or severe grade GVHD. Severity of cGVHD was determined according to the National Institutes of Health criteria [2]. Diagnosis of GVHD was established by histopathology in 4 patients (biopsy of skin, mucosa, or liver). Cardiologic parameters evaluated included electrocardiography, echocardiography, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and systematic clinical follow-up. Severity of PE was classified by its size based on echocardiographic assessment as mild (<10 mm), moderate (10–20 mm), or large (>20 mm). Cytometric analysis of lymphocyte subpopulations in peripheral blood was performed in all patients.

RESULTS

Demographic Data, Disease

PE was diagnosed in 6 patients (aged 20–56 years; median, 38) within 4 to 23 months after allo-HSCT. There were 2 patients with acute myeloid leukemia, 1 with acute lymphoblastic leukemia, 1 with myelodysplastic syndrome, 1 with chronic myeloid leukemia, and 1 with aplastic anemia.

Risk Factors for Occurrence of PE

Before transplant, cardiac function was assessed by echocardiography in all patients, and none of the patients who subsequently developed PE had significant abnormalities found during initial cardiac evaluation. None of them exceeded the dose of anthracyclines >250 mg/m^2 prior to HSCT and none had renal disorders. Four patients were diagnosed as having endocrine disorders, including compensated hypothyroidism (2 patients), hyperprolactinemia (1 patient), and iatrogenic ovarian insufficiency (3 patients). Iron overload was detected in all patients.

Two patients received transplants from HLA-identical siblings and 4 received transplants from unrelated donors, including 2 from mismatched unrelated donors. Five patients received full intensity preparative regimens: 2 received total body irradiation at a dose of 1200 cGy combined with cyclophosphamide, 2 received fludarabine and busulfan, 1 received busulfan combined with cyclophosphamide, and one patient received immunoablative regimens (treosulfan plus cyclophosphamide). Donor lymphocyte infusions were not used.

Four patients demonstrated cytomegalovirus reactivation and were successfully treated prior to the onset of PE. None of them had a history of Epstein-Barr virus reactivation.

One patient had aspergillosis of the heart 1 month prior to presentation of PE. Infection with *Aspergillus fumigatus* was histopathologically confirmed.

Occurrence of Acute and Chronic GVHD

Four patients had acute GVHD preceding the development of PE. All patients suffered from severe cGVHD with involvement of at least 2 other organs (most frequently skin and liver). Diagnosis of GVHD was confirmed histopathologically in 4 patients (biopsy of skin, mucosa, or liver). All patients had active manifestation of cGVHD at the time PE detection.

Presence of fluid in pericardium was confirmed in all patients (4 with large severity, 1 with moderate, and 1 with mild) with concomitant reduction in ejection fraction (EF) of left chamber (minimum 30%–58%) and relaxation impairment. All patients demonstrated signs of grade II or III heart insufficiency according to New York Heart Association.

All patients had elevated NT-proBNP >1000 pg/mL (N < 1250 pg/mL). There were no major changes in electrocardiogram. Cytometric analysis of lymphocyte subpopulations in peripheral blood showed elevated cytotoxic T cell counts in 4 patients (N = 420–660/μL).

Therapy

All patients were receiving systemic immunosuppression at the time of development of PE (usually calcineurin inhibitor: cyclosporine A or tacrolimus), 3 were receiving corticosteroids, and 1 patient was tapering off his immunosuppression before PE detection.

All patients required intensive immunosuppressive treatment and heart function-improving drugs (diuretic, angiotensin-converting enzyme inhibitor, beta-blocker, or aldosterone receptor antagonist). The patient with aspergillosis of the heart required fenestration and pericardium drainage to alleviate incipient cardiac tamponade. An initial antifungal treatment with the combination of voriconazole and caspofungin was not effective, therefore, therapy was successfully changed to liposomal amphotericin B.

Treatment resulted in general status improvement, increased EF, improvement in left ventricular systolic function, and reduction of PE (2 complete resolutions of effusion and 3 reductions in effusion size [2 mild and 1 moderate severity]). Constrictive pericarditis has developed in 1 patient.

Only 1 patient improved following corticosteroids only, while others required complex approaches including tacrolimus plus sirolimus, rituximab, and extracorporeal