A case of cardiac localization of graft-versus-host disease after allogenic bone marrow transplantation

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A 29-year-old male developed symptoms and signs of heart failure shortly after allogenic bone marrow transplantation for chronic myelogenous leukemia. Echocardiographic evaluation showed left ventricular wall thickening, a left ventricular restrictive filling pattern and pericardial effusion. Cardiac magnetic resonance revealed nodular areas compatible with lymphocyte infiltration. The hypothesis of cardiac graft-versus-host disease was supported by the reversibility of all the abnormalities after specific treatment.

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Case report

A 29-year-old male with chronic myelogenous leukemia received, after treatment with cyclophosphamide and total body irradiation (1200 cGy), an allogenic bone marrow transplantation from an HLA-identical sibling. No heart disease was found at pretreatment ECG and echocardiography (Table I) and no ECG changes occurred after treatment. Before and after transplantation, the patient was treated with cyclosporine A and methotrexate to prevent graft-versus-host disease (GVHD).

An erythematous rash on the anterior chest wall appeared 20 days after engraftment. It disappeared within 24 hours of the initiation of steroid treatment.

Fifty-three days later, fever and leucopenia were noted. The patient was hospitalized but neither bacterial nor viral infection was found. An inflammatory cerebral lesion was detected at magnetic resonance requested after the detection of a hypodense lesion at computed tomography. Two days later the patient developed dyspnea, and a transthoracic echocardiography showed uniform thickening of the left ventricular (LV) wall with a normal ejection fraction, a LV restrictive filling pattern at mitral Doppler analysis and moderate pericardial effusion without cardiac tamponade (Table I). The myocardial echocardiographic texture was inhomogeneous with a "starry sky" aspect (Figs. 1A and 1C, 2A and 2C). Magnetic resonance showed LV wall thickening, with irregular endocardial borders, and focal areas of hypodensity, which were more evident on the septal and diaphragmatic segments. The patient underwent a bone marrow examination which revealed that there was no morphological or cytogenetic relapse of chronic myelogenous leukemia.

Since these echocardiographic findings could be explained by a cardiac localization of a GVHD, a therapeutic regimen including higher doses of steroids was started. The patient clinically improved after graft treatment and the dyspnea disappeared within 3 weeks.

An echocardiographic follow-up was performed at 3 months and normalization of the wall thickness and filling pattern was found; the pericardial effusion had rapidly resolved (Figs. 1B and 1D, 2B and 2D, Table I). Computed tomography confirmed that even the cerebral lesion had completely resolved.

Discussion

The main finding in this case is the unusual cardiac involvement and we hypothesized that this was consequent to an acute GVHD. The development of GVHD is generally due to the result of the reaction of donor T lymphocytes with the minor histocompatibility antigens of host tissues[1].

Table I. Changes in echocardiographic parameters.

	Screening echo	Echo at symptoms	Follow-up echo
IVS (cm)	0.65	1.28	1.09
LVEDD (cm)	5.30	4.44	5.13
PW (cm)	0.74	1.16	0.91
EF (%)	60	61	66
E/A ratio	0.81	2.9	0.90
DT (ms)	160	115	148
PE	No	++	No

Screening echo = performed before bone marrow transplantation; Echo at symptoms = performed 53 days after bone marrow transplantation; Follow-up echo = performed 4 months after bone marrow transplantation. DT = deceleration time of the E wave at Doppler mitral flow; E/A = mitral E/A ratio at Doppler mitral flow; EF = ejection fraction; IVS = interventricular septum; LVEDD = left ventricular end-diastolic diameter; PE = pericardial effusion; PW = left ventricular posterior wall.

Lymphocyte infiltration could be present in the most frequently involved tissues in acute GVHD (skin, liver, and gastrointestinal tract).

The patient had clinical symptoms due to an impaired myocardial contractile function and we would have expected that these were related to chemotherapy toxicity[2]. The most frequent aspect of cardiac involvement after chemotherapy is a global LV dysfunction, with a reduced ejection fraction. Anthracyclines are the agents that more frequently cause cardiac injury by a direct myocardial damage. The mean onset of symptoms reported by several studies is 4 weeks with a range of 1-17 weeks[3-5]. Our patient was treated with cyclophosphamide, which can induce acute cardiotoxicity with a reduced global cardiac function[6]. Cardiotoxicity has not been reported for the other two agents administered to this patient (i.e. cyclosporin A and methotrexate). Another possible cause of dyspnea in bone marrow transplanted patients is pericardial effusion due to both chemotherapy and total body irradiation. In our patient, a moderate pericardial effusion was found but no clinical or echocardiographic signs of cardiac tamponade were present.

Our main echocardiographic findings were a LV wall thickening and an impaired LV filling with a normal ejection fraction. These findings support the hypothesis of an infiltrative cardiomyopathy and do not seem to be related to drug toxicity. Myocardial hypertrophy has recently been described in patients treated with cyclosporin for the prevention of GVHD. In these patients hypertrophy was an echocardiographic finding but no clinical signs were present[7]. Cardiac magnetic resonance confirmed the presence of nodular areas probably due to lymphocyte infiltration.

Neoplastic myocardial infiltration in acute monoblastic leukemia or lymphoma has been previously reported as an autoptic finding in advanced stages of the disease[8,9]. In our patient, the hypothesis of the reactivation of the primary disease was not supported by hematological and bone marrow findings.

Myocardial biopsy was not performed to rule out acute viral myocarditis. Polymorphous and non-spe-

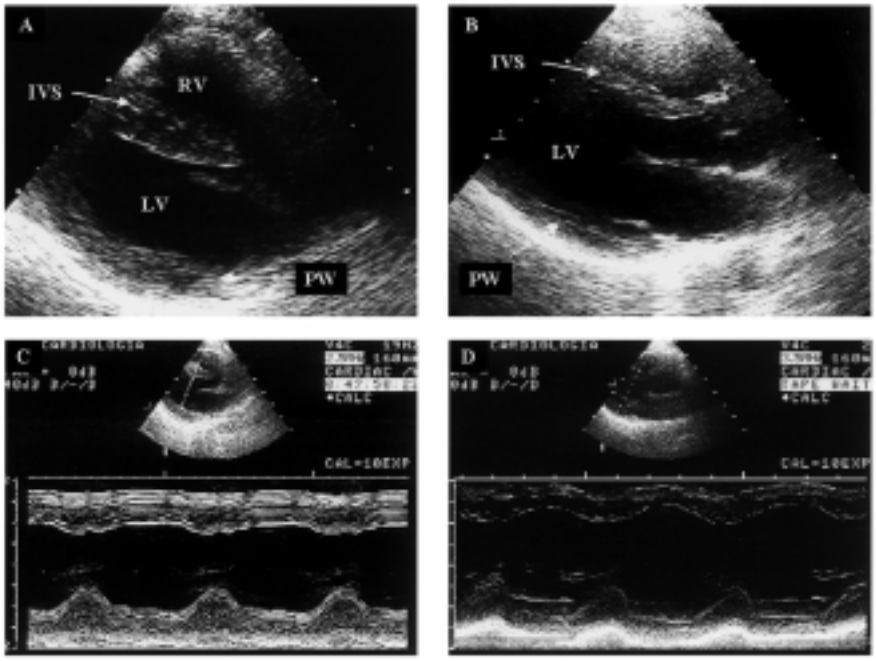

Figure 1. *Comparison between echocardiographic examinations at different moments of the clinical course. Two-dimensional and M-mode images on the parasternal long-axis views showed a wall thickening and reduced diameters of the left ventricle (LV) at the time of symptom onset* (A *and* C). *After graft treatment, the wall thickness and cavity dimensions returned to normal* (B *and* D). *IVS = interventricular septum; PW = left ventricular posterior wall; RV = right ventricle.*

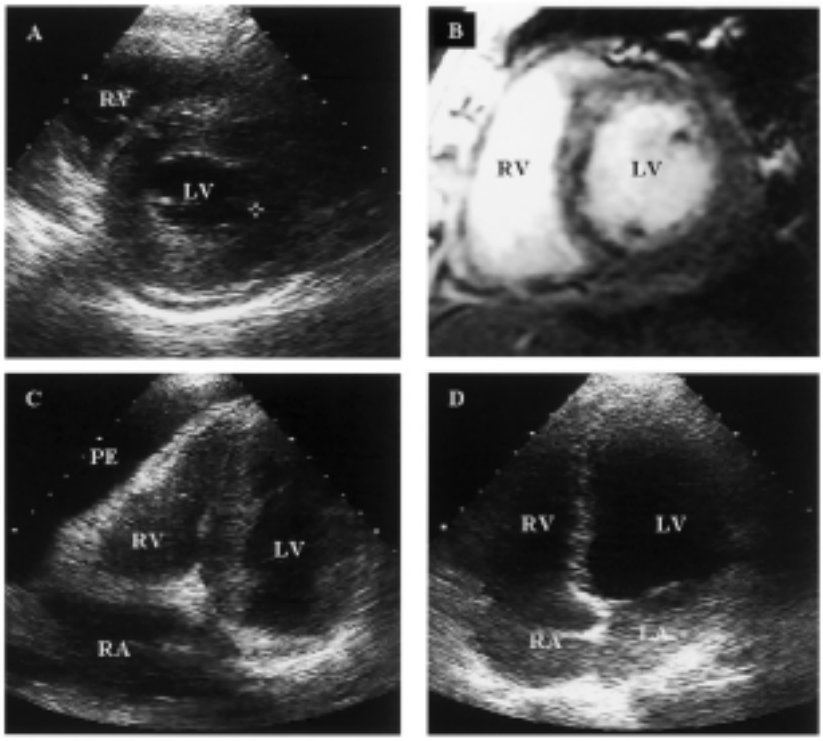

Figure 2. *The parasternal short-axis and 4-chamber views at the time of symptom onset showed wall thickening* (A *and* C). *A pericardial effusion (PE) was present and more evident adjacent to the right ventricular free wall* (C). *Magnetic resonance at the time of symptom onset showed an inhomogeneous texture with small hyperdense areas* (B). *Both the increased wall thickness and PE resolved after graft treatment* (D). *LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.*

cific echocardiographic findings have been described in acute myocarditis and both an increased wall thickness and pericardial effusion have been reported. Otherwise, LV systolic dysfunction is the most common finding reported in previous studies[10,11] but was not present in our patient. Echocardiographic abnormalities and symptoms completely disappeared after steroid treatment that is a consolidated therapy for GVHD whereas it seems to be ineffective in acute myocarditis[12,13].

To our knowledge, this is the first report of a cardiac GVHD including diastolic dysfunction after bone marrow transplantation. In the two other papers that described cardiac GVHD, lymphocyte infiltration caused complete heart block[14] or severe acute systolic dysfunction[15]. Massive lymphocyte infiltration of both the myocardium and pericardium has been described even in the only other comparable situation, i.e. host-versus-graft reaction after heart transplantation[16].

The occurrence of echocardiographic changes after transplantation, the presence of skin GVHD, the presence of another possible localization of GVHD (the cerebral lesion detected at nuclear resonance) and the resolution after treatment support our hypothesis of cardiac GVHD.

Echocardiography was determinant for the diagnosis and it guided us in deciding the etiology of cardiac failure and, consequently, the most appropriate treatment.

References

1. Klingebiel T, Schlegel PG. GVHD: overview on pathophysiology, incidence, clinical and biological features. Bone Marrow Transplant 1998; 21 (Suppl 2): S45-S49.
2. Brockstein BE, Smiley C, Al Sadir J, Williams SF. Cardiac and pulmonary toxicity in patients undergoing high-dose chemotherapy for lymphoma and breast cancer: prognostic factors. Bone Marrow Transplant 2000; 25: 885-94.
3. Iarussi D, Indolfi P, Galderisi M, Bossone E. Cardiac toxicity after anthracycline chemotherapy in childhood. Herz 2000; 25: 676-88.
4. Moreg JS, Oglon DJ. Outcomes of clinical congestive heart failure induced by anthracycline chemotherapy. Cancer 1992; 70: 2637-41.
5. Shan K, Lincoff AM, Young GB. Anthracycline-induced cardiomyopathy. Ann Intern Med 1996; 125: 47-58.
6. Ayash LJ, Wright JE, Tretyakov O, Gonin R, Elias A. Cyclophosphamide pharmacokinetics: correlation with cardiac toxicity and tumor response. Clin Oncol 1992; 10: 995-100.
7. Espino G, Denney J, Furlong T, Fitzsimmons W, Nash RA. Assessment of myocardial hypertrophy by echocardiography in adult patients receiving tacrolimus or cyclosporine therapy for prevention of acute GVHD. Bone Marrow Transplant 2001; 28: 1097-103.
8. Furihata M, Ido E, Iwata J, et al. Adult T cell leukemia/lymphoma with massive involvement of cardiac muscle and valves. Pathol Int 1998; 48: 221-4.
9. Iemura A, Yano H, Kojiro M, Nouno R, Kouno K. Massive cardiac involvement of adult T-cell leukemia/lymphoma. An autopsy case. Arch Pathol Lab Med 1991; 115: 1052-4.
10. Pinamonti B, Alberti E, Cigalotto A, et al. Echocardiographic findings in myocarditis. Am J Cardiol 1988; 62: 285-91.

11. Felker GM, Boehmer JP, Hruban RH, et al. Echocardiographic findings in fulminant and acute myocarditis. J Am Coll Cardiol 2000; 36: 227-32.
12. Garg A, Shiau J, Guyatt G. The ineffectiveness of immunosuppressive therapy in lymphocytic myocarditis: an overview. Ann Intern Med 1998; 129: 317-22.
13. Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. N Engl J Med 1995; 333: 269-75.
14. Gilman AL, Kooy NW, Atkins DL, et al. Complete heart block in association with graft-versus-host disease. Bone Marrow Transplant 1998; 21: 85-8.
15. Platzbecker U, Klingel K, Thiede C, et al. Acute heart failure after allogeneic blood stem cell transplantation due to massive myocardial infiltration by cytotoxic T cells of donor origin. Bone Marrow Transplant 2001; 27: 107-9.
16. Loire R, Tabib A. Early fatal lesions after cardiac transplantation. Results of 100 autopsies. Arch Mal Coeur Vaiss 1993; 86: 19-25.