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High Incidence of Pericardial Effusion in Non-Hodgkin's Lymphoma: Usefulness of Echocardiography*

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Abstract—*In a consecutive group of patients with non-Hodgkin's lymphoma a prospective study was designed to detect pericardial and myocardial abnormalities at presentation for initial clinical staging. Thirty-two patients, ranging from 15 to 65 (mean, 46) years of age, were studied. Twenty-six (81%) were in Stages III and IV. Echocardiographic examination revealed that 17 patients (53%) had pericardial effusion (PE). Four subjects with lymphoblastic lymphoma and extensive mediastinal involvement had clinical and echographic signs of cardiac-tamponade. In 5 cases, pericardiocentesis was performed; abnormal lymphoblasts were demonstrated in 4. In one of these, the histological diagnosis of lymphoma was performed from analysis of the PE. The follow-up ranged from 3 to 32 (mean, 12.3) months. There was no difference in the survival rates whether or not PE was present: 70 and 68% respectively at 1 yr. No patient required intracavitary chemotherapy or surgery. We conclude that PE in advanced non-Hodgkin's lymphoma with large mediastinal masses is frequent. Once tamponade is treated, the presence of PE has no adverse effect on survival at 1 yr.*

INTRODUCTION

PERICARDIAL effusion (PE) is not a frequent initial clinical finding in patients with lymphomas. While Kaplan in 1972 [1] reported PE in only 5 of 340 patients with Hodgkin's disease, in necropsy series the incidence is somewhat larger. Cardiac or pericardiac infiltration was found by Roberts *et al.* [2] in 24 out of 196 autopsies of all histological types of lymphomas, and Rosenberg *et al.* [3] found it in 63 of 277 necropsies of patients with non-Hodgkin's lymphomas.

The scarcity of clinical signs of pericardial compromise at the initial diagnostic staging of these patients limits the value of the physical examination. In a recently published series of 13 patients, most of them having Hodgkin's disease [4], echocardiography proved to be a valuable diagnostic tool for detecting PE in 6 patients prior to treatment.

In the present work we report 32 patients with non-Hodgkin's lymphoma studied using M-mode and two-dimensional echocardiography to investigate the frequency, mechanism and clinical course of their PE.

MATERIALS AND METHODS

Thirty-two consecutive patients with non-Hodgkin's lymphoma from the lymphoma unit at the Hospital Universitario de Caracas were evaluated between January 1978 and January 1981. Sixteen of those studied were men; the mean age was 46 yr (range, 15–76). All patients were clinically staged according to our protocol [5] and classified by the Ann Arbor staging system [6]. Twenty-six patients were in Stages III and IV, and only 6 patients were in Stage II. The biopsy material was classified according to Rappaport [7]. Clinical cardiac examination, electrocardiogram and echocardiogram were

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performed before and after 2 cycles of chemotherapy.

Echocardiography

M-mode echocardiograms were performed with an Ekoline 21 Smith–Kline instrument using a 2.25 MHz transducer 13 mm in diameter, with a beam collimation at 7 cm in depth, and two dimensional echocardiograms were performed with an 81° mechanical sector scan.

All patients were studied in the left lateral decubitus position and their head slightly raised. The transducer was placed in the standard echographic position in the third, fourth or fifth left parasternal intercostal space.

Two-dimensional echocardiographic images of the parasternal long and short axes, apical 4 and 2 chambers, and subcostal views were also obtained [8].

Left ventricular function was calculated by the percentage fractional shortening; normal values ranges from 30 to 45%. The amount of pericardial fluid was determined by the method described by Horowitz *et al.* [9]: *normal* when the two layers of the posterior pericardium followed the same anterior systolic movement; *small effusion* (*ca.* 100 ml) when the visceral and parietal layers of the posterior pericardium remained separated in diastole by 1 mm; *moderate effusion* (approximately 500 ml) when the separation between both posterior pericardial layers was less than 1 cm associated with an echo-free anterior space; and *large effusion* (1 litre or more) was recognized when both an anterior and posterior pericardial echo-free space of more than 1 cm each were present. Pericardial thickening had a pattern when both posterior pericardial leaflets moved together as thick echoes [10]. Echocardiographic signs of hemodynamically significant effusion were present when the right ventricle narrowed at the end of diastole and end of expiration 7 mm or less, showing also inverse phasic respiratory changes of the ventricular cavities [11]. Tamponade, however, was diagnosed on clinical grounds (hypotension, tachycardia, dyspnea, increased venous pressure, paradoxical pulse).

Chest roentgenograms

The pleural effusions seen on the chest X-ray films were classified in the following manner: (a) *small effusion*: blunting of the costophrenic angle seen on the lateral film; (b) *moderate effusion*: blunting of the costophrenic and cardiophrenic angles with a superior concave curve; (c) *large effusion*: all previous criteria plus mediastinal shift [12].

Morphologic study and histochemical stain

Pericardial cell suspensions were obtained with a cytospin cytocentrifuge (Shandon Southern, Cheshire, England) at 1500 rev/min for 5 min. Wright and acid phosphatase stains were used [13].

All pericardiocenteses were performed by the subxiphoid approach with the patient almost seated. More than 500 ml of fluid was drained in each of the 5 patients on whom pericardiocentesis was performed. Heparin was used to avoid clotting.

Treatment

Twenty-five patients received a chemotherapy combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) [14]. Four patients with lymphoblastic lymphoma were treated with the regimen outlined by Murphy *et al.* (Modified CHOP) [15], and one patient with nodular lymphocytic well-differentiated (NLWD) and another subject with nodular mixed lymphoma (NML) received cyclophosphamide, vincristine and prednisone (COP) [16]. One patient suffering from ischemic heart disease having a high risk for cardiotoxicity was treated with cyclophosphamide, vincristine, procarbazine and prednisone (C-MOPP) [17]. The patients with cardiac tamponade were tapped; in addition to chemotherapy they received palliative radiation of 2000 rad to the mediastinum for 12 days.

Statistical analysis

Survival rates were calculated from the date of initiation of therapy to death using the technique of Kaplan and Meier [18]. Statistical chi-square evaluation of small numbers of patients in various groups was done with 2×2 contingency tables [19]. Non-paired ± statistics for two means were also calculated.

RESULTS

Clinical presentation

Twenty-six subjects (81%) were clinically in Stages III and IV at the time of admission, including all 17 patients with PE. The clinical features of the patients with PE are summarized in Table 1. Ten of the 17 (58%) had mediastinal or hilar masses; another 10 of the 17 subjects had pleural effusion. Half of the patients with large PE had lymphoblastic lymphoma.

Clinical course

All 17 patients were evaluated clinically and by echocardiography 2 months after therapy.

Table 1. Clinical characteristics of 17 patients with pericardial effusion in non-Hodgkin's lymphomas

Case No.	Age (yr), sex	Pathologic type*	Clinical stage	P.E.† size	Chest X-ray findings of pleural effusion‡ MM§	HM‖	Survival (months)
1	76, F	DHL	IV	L	S	—	3
2	62, M	DHL	IV	L	L	—	10+
3	58, F	DLPD	IV	L	—	M.M.	3
4	22, F	LL	IV	L	L	M.M.	24
5	65, F	DML	III	L	—	M.M.	13
6	15, F	LL	III	L	L	M.M.	36
7	19, M	LL	IV	L	L	M.M.	9+
8	29, F	LL	IV	L	L	M.M.	15
9	17, M	DHL	IV	M	—	—	18+
10	40, M	DHL	III	M	—	—	3
11	56, M	DLPD	IV	M	S	—	12+
12	25, M	DHL	IV	M	—	—	4+
13	73, M	DHL	III	M	M	M.M.	3
14	65, F	DLPD	IV	M	—	—	3+
15	53, F	DHL	IV	S	S	M.M.	24+
16	55, M	DML	IV	S	S	M.M.	36
17	55, F	NLWD	IV	S	—	H.M.	18

*Pathologic type: DHL: diffuse histiocytic lymphoma; DLPD: diffuse lymphocytic poorly differentiated lymphoma; DML: diffuse mixed lymphoma; LL: lymphoblastic lymphoma; NLWD: nodular lymphocytic well-differentiated lymphoma.

†Pericardial effusion size: large: 1000 ml or more; moderate: around 500 ml; small: 100 ml.

‡Pleural effusion: small: blunting of the cardiophrenic angle on the lateral film; moderate: the above plus blunting of the cardiophrenic angle with superior concave curve; large: all of the above criteria and mediastinal shift.

§MM: Mediastinal mass.

‖HM: Hilar mass.

In 12 of them (70%) there was no evidence of PE, including the 4 subjects with cardiac tamponade. This corresponded with a general remission of the disease. In one patient the PE decreased to about half, while in 3 patients with no response to therapy the PE remained the same. One patient was lost to follow-up (see Table 2). None had echographic pericardiac thickening. The patients were followed from 3 to 36 (mean 12.3) months. There was no difference whether or not the patients had PE on one-year survival, complete remission (35%

Table 2. Treatment of the pericardial effusion and response after two months follow-up

No. of patient	Size of PE*	Treatment	Response
4	Large	CHOP + RT‡	No evidence of PE
1	Large	CHOP§	No evidence of PE
3	Large	CHOP§	No change
4	Moderate	CHOP§	No evidence of PE
1	Moderate	C-MOPP‖	Decreased 50%
1	Moderate	CHOP§	Lost to follow-up
2	Small	CHOP§	No evidence of PE
1	Small	COP¶	No evidence of PE

*Pericardial effusion.

†Modified CHOP according to Murphy *et al.* [15].

‡Palliative mediastinal radiotherapy (2000 rad).

§CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone.

‖C-MOPP: Cyclophosphamide, vincristine, procarbazine, prednisone.

¶COP: Cyclophosphamide, vincristine, prednisone.

and 36%) or remission duration (15 and 16 months) respectively.

Echocardiographic findings

Pericardial effusion was demonstrated by echocardiography in 17 patients (53%); it was suspected clinically in 4 subjects and suggested by the chest roentgenogram in 3. The PE was large in 8 patients, moderate in 6 and small in 3 (Table 1).

Left ventricular function studied by the percent fractional shortening was normal in 13 patients with PE and in 15 patients without PE; 34 ± 6.3 (S.D.) and 35 ± 6 respectively. Fractional shortening was not calculated in the 4 patients with pericardial tamponade.

Correlation between the PE and the presence of hilar or mediastinal masses

Ten subjects had both PE and hilar/mediastinal masses, but 7 had PE without hilar/mediastinal masses. Six patients studied with hilar/mediastinal masses had no PE, whereas 9 subjects had neither PE nor hilar/mediastinal masses. None of these relationships have statistical significance ($\chi^2 = 0.50$). Six of 8 subjects with large PE had masses.

Serum albumin

There was no significant statistical difference between the serum albumin of the patients with or without PE: 3.40 ± 0.67 and 3.72 ± 0.98 g/dl respectively ($P = 0.10$).

Characteristics of the pericardial fluid

Five subjects had pericardiocentesis on admission; 4 of these, all of whom had lymphoblastic lymphoma, had signs and symptoms of cardiac tamponade.

The pericardial fluid of all five patients clotted spontaneously. Four were hemorrhagic and showed lymphoblasts with neoplasic changes on cytologic examination. In one patient with no suitable adenopathy for biopsy the abnormalities demonstrated by the fluid cytology were the only histologic evidence for lymphoblastic lymphoma.

The PE-cytocentrifuged cell blocks had the characteristic pattern for T lymphocytes on the acid phosphatase stain. In one subject the fluid had increased mesothelial cells with no signs of malignancy. This patient had a diffused mixed cell lymphoma (DML) with a mediastinal mass but no pleural effusion.

DISCUSSION

In this prospective study, more than half of 32 patients suffering from advanced non-Hodgkin's lymphoma had an echocardiographic pericardial effusion at their initial clinical staging; most of them were clinically unsuspected. It is well-known that cardiac ultrasound is very sensitive in detecting even minute amounts of pericardial fluid [9]. This might explain the infrequency of this finding in previous reports where echocardiography was not available [20–24].

We found that the association between mediastinal or hilar masses and large pericardial effusion was frequent; this was not the case in those patients whose effusion was of small or moderate size (Table 1). This is in agreement with the findings of Markiewicz *et al.* [4]. Most of their subjects, however, had Hodgkin's disease, which is known to have more than twice as much mediastinal involvement as non-Hodgkin's lymphoma [25].

Lymphomatous infiltration of the pericardium was of clinical significance in 8 of our subjects with large effusion. It was necessary to perform pericardiocentesis in 5: in 4 because of cardiac tamponade, and in 1 for diagnosis. It is noteworthy that abnormal lymphoblasts were found in 4 patients with lymphoblastic lymphoma and large mediastinal masses.

Our findings are in agreement with those of Lichtenstein *et al.* [26], who reported that 5 out of 17 patients with primary mediastinal lymphoma had pericardial involvement, and 4 of these had lymphoblastic lymphoma.

In a necropsy series of 17 lymphomas (9 of them non-Hodgkin's lymphoma) there was radiologic evidence of pleural, mediastinal or lung infiltration, suggesting that the pericardial compromise was an extension of the disease [20]. Therefore, the association of pleural effusion, as well as mediastinal or hilar masses, with the pericardial effusion suggests that abnormalities in the lymphatic and venous drainage of the mediastinum and direct pericardial infiltration play a significant role in their origin. Nevertheless, pericardial effusion appeared without mediastinal masses in 2 of our subjects. Levitt *et al.* [27] described a patient with cardiac tamponade as a primary manifestation of lymphosarcoma cell leukemia, with no mediastinal compromise [27]. In our series 46% of the patients with DHL had PE, whereas none had any evidence of sclerosis in the biopsies reviewed, even though this could have been suggested by findings of Miller *et al.* [28], where this type of histology was associated with superior vena-cava obstruction syndrome or mediastinal disease. The presence of hypoalbuminemia was of significance in our series.

The clinical and echocardiographic disap-

pearance of the fluid correlated best with the clinical improvement in each patient. We did not need to use intracavitary chemotherapy or surgery. We suggest that when a large mediastinal mass is associated with pericardial effusion the combined treatment of chemotherapy in conjunction with mediastinal radiation is the treatment of choice.

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