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PRIMARY CHYLOPERICARDIUM WITH PULMONARY SHADOW AND LARGE GRANULAR LYMPHOCYTOSIS: A Case Report

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ABSTRACT

A 79-year-old man with primary chylopericardium associated with large granular lymphocytosis was followed for more than 26 years. Except for development of dyspnea on exertion during the past four years and more recently cough with sputum production, he has remained largely asymptomatic over this interval. Based on detailed examinations of cellular and humoral immunity, we speculate that increased natural killer cell activity and an increased number of large granular lymphocytes circulating in his peripheral blood represent a reactive response to production of various cytokines secondary to persistent loss (? chyloptysis) and sequestration of central lymph.

Primary chylopericardium is a disease in which a pericardial effusion rich in chylomicra develops due to an abnormal communication between the central lymphatic system and the pericardial cavity. Although the pathogenesis is often obscure, it is noteworthy that patients undergoing chronic thoracic duct drainage develop depression of T lymphocytes and a proportional increase in B lymphocytes (1-4). Although detailed immunologic derangements have been described in patients with chyluria (5-7) and chylothorax (8), cellular and humoral immune function with chylopericardium has scarcely been examined (9,10). We now report a patient with primary chylopericardium who has been followed for more than 25 years. Over this long period of observation, other than dyspnea on exertion, he has remained largely asymptomatic. The chylopericardium has been associated with a pulmonary shadow, large granular lymphocytosis and other normal and abnormal immunological findings.

Case Report

A 79-year-old man was periodically followed for 26 years. In 1962, enlargement of the cardiac shadow was seen on routine chest x-ray, but no treatment was instituted. Beginning in March 1982, he developed exertional dyspnea. On chest x-ray, enlargement of the cardiac shadow and Kerley B lines were noted, and the patient was admitted for possible congestive heart failure. An echocardiogram revealed a pericardial effusion. Pericardial aspiration yielded a milky-white fluid abundant in chylomicra. Three years later, yellow sputum first appeared, a shadow was observed in the lower right lung field on a chest x-ray in early 1986, and exertional dyspnea worsened over the ensuing two years. There was no other notable medical illness in the past and specifically no prior operation. A younger sister had died of

bronchial asthma. At this time, there was no mental or neurological dysfunction. The blood pressure was 154/82mmHg, the pulse rate was 66/min and regular. There was no swelling, paradoxical pulse or jugular venous distension. Superficial lymph nodes were not palpable. He had no rash. Although moist rales were heard in the lower right lung field, no cardiac murmur or pericardial friction rub was detected. The liver and spleen were non-palpable.

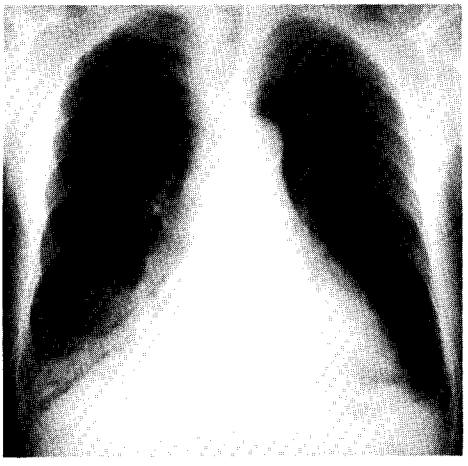

Fig. 1. Chest roentgenogram. The cardiac shadow is enlarged and an interstitial infiltrate (shadow) is seen in the right lower lung field.

Laboratory findings indicated the urinalysis and hemogram were normal. The C-reactive protein (CRP) and erythrocyte sedimentation rate were both unremarkable. Serum cholesterol and neutral fats were within normal limits. Arterial blood gas analysis showed decreased PaO_2 with an obstructive component as indicated by respiratory function tests. On chest x-ray, the cardiothoracic ratio was 56% and an infiltrate was seen in the lower right lung field *(Fig. 1)*. Oil-contrast lymphography demonstrated a narrowing of the thoracic duct adjacent to the origin of the fifth rib without lymph node swelling or filling defect.

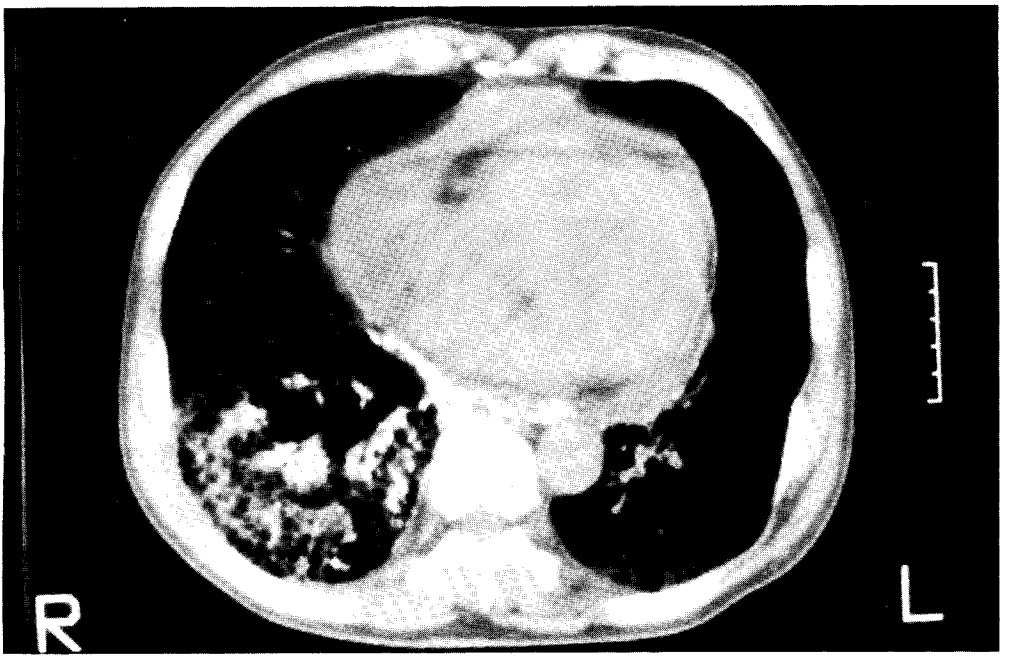

Fig. 2. Chest computer tomography taken one week after conventional lymphography. Note the "white" oil contrast filling both the peribronchial lymph ducts in the right lower lung field and the pericardial cavity.

Chest computer tomography taken one week after conventional lymphography showed retrograde flow of the oil-contrast into the peribronchial lymph ducts in the lower right lung field and pericardial cavity. Gallium (Ga) scintigraphy failed to show abnormal tracer accumulation. Accordingly, the diagnosis was made of primary chylopericardium with an associated pulmonary "shadow" *(Fig. 2)*.

In the peripheral blood, the red blood cell count was $456x10^4/\mu l$, neutrophils were 63%, lymphocytes 32% with more than 50% of them being large granular lymphocytes. Serum immunoglobulin and complement levels were normal: IgG 1681mg/dl, IgM 194mg/dl, IgA 82mg/dl; CH_{50} 34.5U/ml, C_3 62.3mg/dl, C_4 23.2mg/dl. The antinuclear antibody was negative. The PPD dermal test was nonreactive and lymphocyte proliferation using phytohemagglutinin, conconvalin A, and pokeweed mitogen disclosed a lowered stimulation index of 27, 16, 9, respectively. A bone marrow aspirate was unremarkable. The level of plasma - interferon was 0.09ng/ml or normal (11). The results of circulating lymphocyte subsets are shown in *Table 1*. In brief, CD3, CD4, CD4/CD8, CD5, $CD4^+45RA^+$ and $CD4^+29^+$ were low, whereas CD11b, CD16, CD57, $CD16^+57^+$, $CD3^-8^+$ and $CD3^-8^-56^+$ were elevated.

Natural killer cell activity of the patient's lymphocytes was increased (44.1%) as assayed by ^{51}Cr release from K562 target (E:T=20:1). Antibody dependent cell-mediated cytotoxic activity was normal (25.9%) as assayed by ^{51}Cr from CRBC target (E:T=20:1).

Gene analyses of peripheral blood T-lymphocyte receptor ß-chain and γ-chain both indicated normal germ lines (13). Specifically, no abnormality was detected in the chromosome test using either peripheral or bone marrow blood cells.

Clinical course

No notable change occurred in either the cardiac or pulmonary shadow on follow-up x-rays. Subjective symptoms remained stable and the patient was treated with expectorants. Neither pneumonia nor heart failure developed and the patient was otherwise functioning well. Throughout the clinical course, the CRP was consistently negative and there was no evidence for viral infection. The large number of granular lymphocytes in the peripheral blood persisted and the NK cell activity remained elevated (64.5%).

TABLE 1
Circulating Subsets of Lymphocytes

CD2(OKT11)	78.0%	CD3(OKT3)	26.9%
CD4(OKT4)	11.9%	CD8(OKT8)	34.2%
CD4/CD8	0.35	CD5(Leu1)	39.5%
CD19(B4)	2.8%	CD20(B1)	9.1%
CD21(B2)	13.0%	SmIg*	7.7%
OKIa	15.9%	IL-2Rα	8.0%
IL-2R ß	72.9%	CD11b(OKM1)	39.5%
CD16(Leu11)	59.8%	CD56 (Leu19)	23.7%
CD57(Leu7)	50.7%	$CD4^+45RA^+$	0.4%
$CD4^+29^+$	9.0%	$CD57^+16^+$	42.7%
$CD3^+4^+$	13.0%	$CD3^+8^+$	19.0%
$CD3^-CD8^+$	21.0%	$CD3^-8^-56^+$	45.0%

*surface membrane immunoglobulin bearing lymphocytes

DISCUSSION

Isolated chylopericardium was first described by Hasebrock in 1888 (14). In 1954, the syndrome of "primary chylopericardium" was first categorized by Groves and Effler (15). Primary chylopericardium is rare, its etiology usually obscure, and, to our knowledge, only some 50 patients with this entity have thus far been reported (16). Although there must be a communication between the pericardial space and the thoracic duct, its exact location has typically not been able to be delineated. In some patients, hygroma (14), lymphangiectasis (17,18), lymphangioma (19), hamartoma (20), and lymphoma (21), are accompanied by chylopericardium.

Chylopericardium associated with a pulmonary abnormality is even rarer but has been described with retrograde flow of oil contrast into the lung after lymphography (18,22), Kerley B lines, and a groundglass-like shadow on the chest roentgenogram (20,23,24). In a patient with chylopericardium without pulmonary involvement, Fujiseki et al (25) observed, after oral intake of ^{131}I-triolein, accumulation of the tracer in the lung. This observation suggested the existence of pulmonary disease despite lack of a visible abnormality on chest x-ray. Dyspnea and sputum production can be secondary to cardiac tamponade and may in this instance relate to the pulmonary abnormality. Our patient remained asymptomatic for >20 years since enlargement of the cardiac shadow was first detected at the age of 53 years. Twenty years later, however, dyspnea commenced and four years thereafter cough and yellow sputum production (? chylo-ptysis) occurred along with an abnormal pulmonary shadow that has persisted.

A persistent loss or sequestration of lymph as with chylopericardium, chylothorax, chyluria, and thoracic duct drainage exerts a deleterious effect on the immune system and especially cellular immunity. Cifferri et al (5), for example, demonstrated that in 3 patients with chyluria, there were decreased lymphocytes, low serum IgA, increased precursor immune cells, decreased lymphocyte response to mitogen stimulation, and reduced levels of CD4, CD4/CD8 in the peripheral blood. In addition, blood levels of CD8, CD11b, and CD56 were high and natural killer cell (NK) activity was low. Charnila et al (9), on the other hand, demonstrated that the T cell and B cell counts in peripheral blood were normal in primary chylopericardium. Bewick and colleagues (10) showed that the helper-suppressor T cell ratio and staining for surface immunoglobulin in peripheral blood were also normal in primary chylopericardium. McWilliams et al (8) demonstrated transient T cell depression in postoperative chylothorax. External thoracic duct drainage was associated with reduced T cell count and proportional increase in B lymphocytes, decreased cell-mediated immunity, and long term skin homograft survival (1-4). In our patient, we found normal levels of serum immunoglobulins, decreased CD3, CD4, and immunoglobulin bearing lymphocytes, increased CD8, CD11b, CD16, CD57 and large granular lymphocytes in peripheral blood, non-reactivity to PPD skin test, and depressed lymphocyte immunoreactivity.

Large granular lymphocytes (LGL) are generally the mononuclear cell population responsible for natural killer activity. By the surface marker, they are chiefly classified into two groups, $CD3^+4^+8^+11^-16^-$ and $CD3^-4^-8^-11^+16^+$ (26-29). Whereas it is often difficult to differentiate "reactivity" from "leukemia" with increased LGL, the data in this instance favors hyperreactivity: the benign clinical course of the patient, lack of either lymph node swelling or hepatosplenomegaly, absence of anemia and chromosomal aberration, patterns of circulating lymphocyte surface markers, and results of gene analysis of T cell receptor ß and γ-chains. Although the pathogenesis of large granular lymphocytosis and increased natural killer cell activity are unclear, these phenomena may represent a release of various cytokines in response to chronic loss or sequestration of central lymph. Further clarification of cellular immunity including

large granular lymphocytosis in primary chylopericardium is warranted.

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REFERENCES

1. McGregor, DD, JL Gowans: The antibody response of rats depleted of lymphocytes by chronic drainage from the thoracic duct. J. Exp. Med. 117 (1963), 303-320.
2. Gowans, JL, JW Uhr: The carriage of immunologic memory by small lymphocytes in the rats. J. Exp. Med. 124 (1966), 1017-1031.
3. McGregor, DD, JL Gowans: Survival of homografts of skin in rats depleted of lymphocytes by chronic drainage from the thoracic duct. Lancet 1 (1964), 629-632.
4. Machleder, HI, H Paulus: Clinical and immunological alterations observed in patients undergoing long-term thoracic duct drainage. Surgery 84 (1978), 157-165.
5. Ciferri, F, AC Bakke, A Lash, et al: Immunologic studies in patients with chyluria. J. Clin. Immunology 5 (1985), 307-313.
6. Date, A, TJ John, KG Chandy, et al: Abnormalities of the immune system in patients with chyluria. Brit. J. Urol. 53 (1981), 384-386.
7. Arnold, WC, RW Steele: Immunodeficiency in congenital chyluria. Pediatrics 56 (1980), 792-794.
8. McWilliams, BC, LL Fan, SA Murphy, et al: Transient T-cell depression in postoperative chylothorax. J. Pediat. 99 (1981), 595-597.
9. Charnila, Y, Y Levo, A Weiss, et al: Isolated idiopathic chylopericardium. J. Thorac. Cardiovasc. Surg. 73 (1977), 719-721.
10. Bewick, D, DE Johnstone, PL Landrigan: Primary chylopericardium associated with allergic alveolitis. Can. Med. Assoc. J. 130 (1984), 1577-1579.
11. Shiozawa, S, K Shiozawa, S Shimizu, et al: Age distribution of circulating α-interferon. Experientia 45 (1989), 764-765.
12. Kamio, M, T Uchiyama, N Arima, et al: Role of α-chain-IL-2 complex in the formation of the ternary complex of IL-2 and high-affinity IL-2 receptor. Int. Immunol. 2 (1990), 521-530.
13. Sangster, RN, J Minowada, N Suciufoca, et al: Rearrangement and expression of the , ß, and chain T cell receptor genes in the human thymic leukemic cells and functional T-cell. J. Exp. Med. 163 (1986), 1491-1508.
14. Hasebrock, K: Analyse einer chylösen pericardialen Flüssigkeit (Chylopericardium). Ztschr. Physiol. Chemie. 12 (1888), 289-294.
15. Groves, LK, DB Effler: Primary chylopericardium. N. Engl. J. Med. 250 (1954), 520-523.
16. Dunn, RP: Primary chylopericardium: A review of the literature and an illustrated case. Am. Heart J. 89 (1975), 369-377.
17. Glasser, SP, MD Cheitlin, LS Salfas, et al: Isolated massive chylopericardium. Am. Heart J. 75 (1968), 663-672.
18. Yoshida, T, T Tomomatsu, et al: Chronic primary chylopericardium: Report of a case with diagnostic interest and review of the literature. Jpn. Circul. J. 33 (1969), 725-733.
19. Goldstein, MR, A Benchimol, W Cornell, et al: Chylopericardium with multiple lymphangioma of bone. N. Eng. J. Med. 280 (1969), 1034-1037.
20. Miller, SU, JH Prutt, A Long: Fatal chylopericardium caused by hamartomatous lymphangiomatosis. Am. J. Med. 26 (1959), 951-956.
21. Barton, JC, JR Durant: Isolated chylopericardium associated with lymphoma. Southern Med. J. 73 (1980), 1551-1552.
22. Motoji, T, K Hiramori, H Nagara, et al: A case of primary isolated chylopericardium. Respiration and Circulation 23 (1975), 447-451.
23. Osamura, Y, S Takahashi, K Hirosawa, et al: A case of primary chylopericardium. Internal Medicine 42 (1978), 141-144.
24. Segawa, Y, K Tamaki, et al: A case of primary chylopericardium. Heart 15 (1983), 85-90.
25. Fujiseki, Y, et al: Non invasive diagnosis

of isolated chylopericardium using precordial pericardial imaging after oral administration of ^{131}I-triolein: Report of a case. J. Cardiography 12 (1982), 553-558.
26. Lanier, LL, AM Le, CI Cirvin, et al: The relationship of CD 16 (Leu-11) and Leu19 (NKH-1) antigen expression on human peripheral blood NK cells and cytotoxic T lymphocytes. J. Immunol. 136 (1986), 4480-4486.
27. Lanier, LL, S Cwirla, N Federspiel, et al: Human natural killer cells isolated from peripheral blood do not rearrange T cell antigen receptor ß chain genes. J. Exp. Med. 163 (1986), 209-214.
28. Abo, T, CA Miller, CM Balch: Characterization of human granular lymphocyte subpopulations expressing HNK-1 (Leu-7) and Leu-11 antigens in the blood and lymphoid tissues from fetuses, neonates and adults. Eur. J. Immunol. 14 (1984), 616-623.
29. Lanier, LL, AM Le, JH Phillips, et al: Subpopulations of human natural killer cells defined by expression of the Leu-7 (HNK-1) and Leu-11 (NK-15) antigens. J. Immunol. 131 (1983), 1789-4796.

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