Natural killer cell-mediated immune deficiency or compromise in patients with portopulmonary hypertension

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Portopulmonary hypertension (POPH) is a form of pulmonary arterial hypertension (PAH) in the setting of portal hypertension, and is associated with a poor prognosis [1]. The underling etiological cause of POPH is poorly understood [1]. Previously we have reported T cell-mediated immune deficiency or compromise in patients with chronic thromboembolic pulmonary hypertension (CTEPH), idiopathic pulmonary hypertension (IPH), and acute pulmonary embolism (APE) [2, 3]. Here we report natural killer cell-mediated immune deficiency or compromise in patients with POPH.

Nine patients (4 male, 5 female) diagnosed with POPH in Shanghai Tongji Hospital from year 2010 to 2011 were recruited in the present study, with a mean age of 65 ±19 years (30–82 years). The diagnosis of POPH is based on the hemodynamic criteria including portal hypertension and/or liver disease (clinical diagnosis) [4], pulmonary artery systolic pressure > 40 mm Hg at rest, pulmonary vascular resistance > 240 dynes × s × cm^{-5}, and pulmonary artery occlusion pressure < 15 mm Hg or transpulmonary gradient > 12 [1]. We firstly detected the cluster of differentiation (CD) on the T cell surface. To our surprise, unlike the changes we previously reported in CTEPH, IPH, or APE, only slight changes of CD3+, CD4+ or CD8+ T cells were observed in POPH patients (Table I and Figures 1 A–C). Interestingly, the number of CD16+CD56, which reflects the function of natural killer cell, was decreased in five patients with POPH (55.6%) (Table I and Figure 1 D) [5].

T cell-mediated immune deficiency or compromise has been reported in patients with CTEPH, IPH, and APE [2, 3]. In the present study, we failed to detect obvious cell-mediated immune changes. Natural killer cells, accounting for 15% of peripheral blood lymphocytes, are well-known unique effectors of the innate immune system as they can recognize stressed cells in the absence of antibodies and MHC [3]. As the role of natural killer cells is analogous to that of cytotoxic T cells [5], we detected their surface markers CD16 (FcγRIII) and CD56 in POPH patients and identified a natural killer cell-mediated immune deficiency or compromise in patients with POPH. Immune deficiency or compromise of natural killer cells is usually caused by virus infection, cancer, or immunosuppressive drugs [5]. In this study, malignant tumors or use of immunosuppressive drugs were excluded in these 9 patients; therefore the immune deficiency or compromise of natural killer cells is most likely due to virus infection.

Our study indicated that the virus-killing function of natural killer cells is compromised in patients with POPH. The POPH might be a disease of

Table I. The etiology, Child-Pugh Class, pulmonary artery systolic pressure, and the clusters of differentiation on T and NK cells of the patients enrolled in this study

Patients	Etiology	Child-Pugh Class	PASP [mm Hg]	CD3+	CD4+	CD8+	CD4/CD8	NKCD16+CD56
Case 1	HBV	Class A	68	77.6	42.7	32.8	1.30	5.3↓
Case 2	HBV	Class B	63	50.0	34.0	10.3↓	3.3↑	6.1↓
Case 3	Cryptogenic	Class B	70	70.7	45.6	24.9	1.83	16.8
Case 4	Autoimmune	Class C	41	45.0↓	25.6↓	19.7	1.30	35.3
Case 5	HBV	Class B	43	61.8	49.8	9.1↓	5.4↑	16.1
Case 6	HCV	Class C	43	67.7	43.7	23.7	1.8	7.4
Case 7	Cryptogenic	Class B	40	66.7	44.5	18.2	2.5	3.4↓
Case 8	HBV	Class B	41	65.3	45.2	14.5↓	3.1↑	6.0↓
Case 9	HCV	Class C	44	66.8	29.5	35.4	0.8	1.9↓

PASP – pulmonary artery systolic pressure, HBV – Hepatitis B virus, HCV – Hepatitis C virus. The normal values of CD3+, CD4+, CD8+, CD4/CD8 and NKCD16+CD56 are (50–80%), (27–51%), (15–44%), (0.71–2.78 : 1) and (7–40%), respectively.

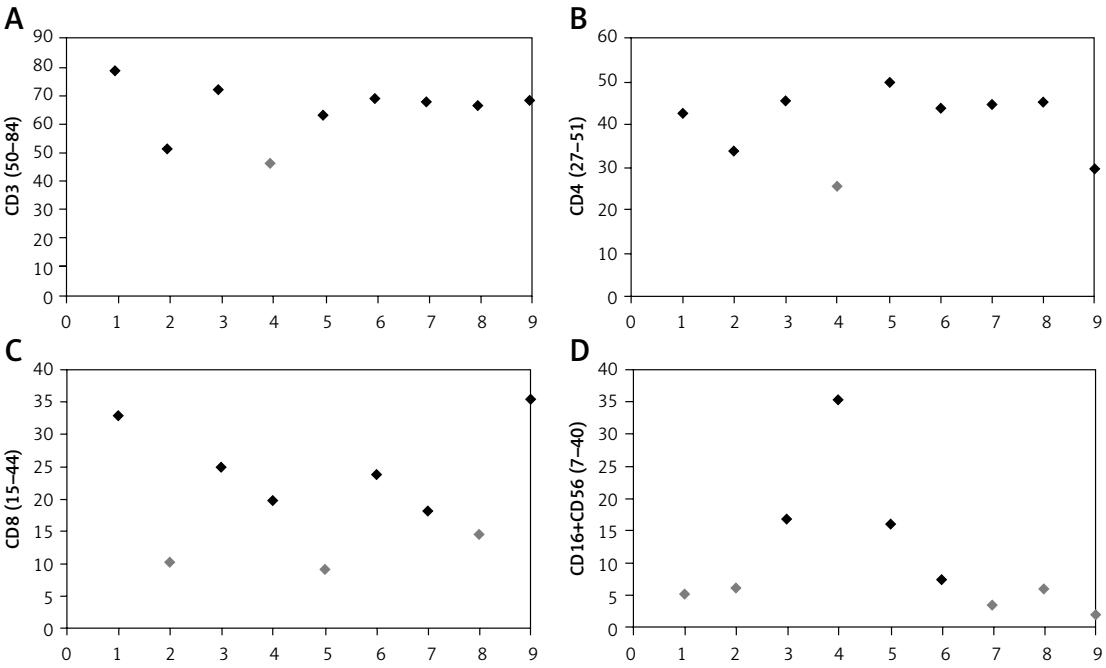

Figure 1. Changes of T and NK cells of the patients enrolled in this study

acquired natural killer cell-mediated immune deficiency, and virus infection may be an important etiological factor of POPH. We also speculate that the pathogenic virus infection in POPH patients may be different from those in CTEPH, IPH, and APE.

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