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## Acute pericarditis: A peculiar manifestation of common variable immune deficiency

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### Abstract

Common variable immune deficiency (CVID) is known as the most prevalent symptomatic inborn error of immunity associated with autoimmune and inflammatory complications in addition to recurrent infections. In this study, we investigated the prevalence of acute pericarditis as a complication in the past medical history of 337 CVID patients. We found five patients (1.5%) that had experienced acute pericarditis, and described the medical history of three patients.

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## Introduction

Common variable immune deficiency (CVID) is a group of inborn immunity errors with an incidence of 1:50,000 to 1:25,000.<sup>1</sup> CVID is characterized by low immunoglobulin (Ig) G and IgA, low to normal IgM serum level along with insufficient antibody responses to both protein and polysaccharide antigens because of defect in B cell differentiation.<sup>2,3</sup> Various clinical symptoms of CVID patients include recurrent infections, enteropathy, lymphoproliferation, and malignancy as well as autoimmune and inflammatory complications.<sup>4</sup> Also, there have been few reports of cardiac manifestations and complications in CVID patients. A literature review shows few report of pulmonary hypertension and pericardial effusion;<sup>5-7</sup> however, there is no report of acute pericarditis, which is defined as inflammation of the pericardial sac, in CVID patients. Acute pericarditis, in general, is of two types: infectious, having bacterial, viral, or fungal etiology, and noninfectious, such as autoimmune, neoplastic, metabolic, etc.<sup>8</sup> In this study, we aimed to find frequency of acute pericarditis in CVID patients, and describe immunological and clinical manifestations of three CVID patients with a history of acute pericarditis and having regular follow-up.

## Methods

We retrospectively reviewed 337 CVID patients, registered in the Iranian Primary Immunodeficiency Registry, from the records of Children's Medical Center Hospital, Tehran, Iran, between 1999 and 2020. Until 2018, information of 3056 primary immunodeficient patients from 31 medical centers was registered in this registry, and the most common category was of patients having predominant antibody deficiency (29.5%).<sup>9</sup> It is estimated that a large number of primary immune deficient patients remain undiagnosed due to the low awareness of primary immunodeficiency (PID) and lack of population-based screening.<sup>10</sup> Hence, the registry statistics do not provide the actual prevalence of immunodeficient patients.

The CVID was diagnosed according to the criteria of the European Society for Immunodeficiencies (ESID) Registry Working Party. We extracted the medical records of CVID patients diagnosed with cardiac problems such as any complaint of chest pain, dyspnea, orthopnea, palpitation, any findings in heart sound, any cardiac complication such as arrhythmia, having echocardiographic finding, or abnormality in electrocardiography. After this, patients with signs and symptoms and data of acute pericarditis were found. The diagnosis of pericarditis was made with at least two of the following four criteria: pleuritic chest pain, new or worsening pericardial effusion, pericardial rub, new widespread ST-segment elevation, or PR depression.<sup>8</sup> For the patients with a history of acute pericarditis, the demographic information (including age, sex, age at onset of symptoms, age at diagnosis, diagnostic delay, consanguinity, and living area), laboratory examinations (complete blood count [CBC], lymphocyte subsets, and serum immunoglobulin levels), and clinical data were collected thru a structured questionnaire. Information of patients with incomplete documentation was collected

through direct interviews. The study was approved by the institutional review board of the Alborz University of Medical Sciences.

## Results

Five CVID patients with a medical history of acute pericarditis were identified from 337 CVID registered patients. Owing to lack of regular follow-up, information of two patients was not complete, so, we report three patients with available past medical history. A brief summary of their demographic, clinical, and immunological features is provided in [Tables 1](#) and [2](#).

### Case descriptions

#### Case 1

This female patient presented with recurrent pneumonia since the age of 3 years. Acute pericarditis and severe pneumonia had occurred for three times: the first episode at the age of 3 years, and the second episode took place twice at the age of 12 years. The second episode was accompanied by moderate pericardial effusion in echocardiography, positive blood culture for streptococcus pneumonia, and high erythrocyte sedimentation rate (ESR = 90). Thorax computerized tomography (CT) scan showed diffused bilateral ground glass opacities with thickening of the bronchial wall and pericardial effusion. Major clinical manifestations included recurrent infectious complications such as otitis media, pneumonia, sinusitis, bronchiectasis, and diarrhea as well as *failure to thrive* (FTT) and hepatosplenomegaly. She died because of respiratory distress and pneumonia at the age of 13 years.

#### Case 2

The patient was a 10-year-old female diagnosed with CVID at the age of 6 years. She experienced recurrent episodes of otitis media, sinusitis, and pneumonia. Pericarditis and pneumonia developed when she was 5 years old, with massive pericardial effusion reported in the echocardiography. Electrocardiography showed sinus tachycardia. She underwent pericardiocentesis and drainage, pericardial fluid was hemorrhagic and turbid. Mild infiltration of mixed inflammatory cells without any malignant cells was reported on pericardium biopsy. After a month, echocardiography revealed good cardiac output without pericardial effusion.

#### Case 3

A 26-year-old female patient, with a history of chronic diarrhea, giardiasis infection, recurrent pneumonia, sinusitis, otitis media, FTT, short stature, and delay in puberty, was diagnosed with CVID in adulthood. At the age of 20 years, the clinical symptoms of orthopnea and pleuritic chest pain, moderate pericardial effusion in the echocardiography, and high serum level of C reactive protein (CRP) were in favor of acute pericarditis. The patient's symptoms improved after five days of hospitalization, and a mild pericardial effusion was reported in echocardiography. After 20 days, echocardiography did not show any pericardial effusion.

**Table 1** Overview of the clinical and immunological findings of the patients with CVID.

No.	Sex	Age (years)	D	AoD (year)	AoO (year)	DD (month)	Consanguinity	Living area	IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)	IgE (IU/mL)	Lymphocyte (% of WBC)	CD3+ T cells (%)	CD4+ T cells, %	CD8+ T cells (%)	CD19+B cell (%)	Cardiac manifestations	Other manifestations
1.	F	10	D	8	3	60	N	R	463	0	32	NA	39	62	24	36	32	Acute pericarditis (three episodes)	Lung abscess, recurrent URIs, recurrent pneumonia, bronchiectasis, gastroenteritis, hepatosplenomegaly, lymphoproliferative disorder and LAP, FTT
2.	F	10	D	6	2	48	Y	U	370	20	41	1	36	68	40	25	21	Acute pericarditis	Recurrent URIs, recurrent pneumonia
3.	F	26	D	21	10	132	N	U	0	6	12	2	19	62	32	31	18	Acute pericarditis	Tooth decay, recurrent URIs, recurrent pneumonia, recurrent gastroenteritis, short stature, delay in puberty, infectious diarrhea (giardiasis), FTT

AOO: age of onset; AOD: age of diagnosis; DD: diagnosis delay; F: female; URIs: upper respiratory infections; LAP: lymphadenopathy; FTT: failure to thrive; N: no; Y: yes; NA: not available; D: dead; R: rural; U: urban.

**Table 2** Clinical and laboratory findings of CVID patients with acute pericarditis.

Patients	Symptoms and physical examination	Echocardiography findings	Laboratory data at the time of pericarditis
1	All episodes: chest pain, dyspnea, fever, cough; pericardial friction rub in the second episode	Pericardial effusion	Second episode: positive blood culture for streptococcus pneumonia, WBC = 21,200 (PMN = 89%), ESR = 90 Third episode: WBC = 10,400 (PMN = 67%). CRP = 3+, ESR = 38
2	Chest pain, dyspnea, orthopnea, fever, cough, tachycardia	Massive pericardial effusion	
3	Chest pain, orthopnea	Mild pulmonary hypertension, pericardial effusion	WBC = 10,380 (PMN = 74%), CRP = 87, ESR = 26

WBC: white blood cells, PMN: polymorphonuclear leukocytes, ESR: erythrocyte sedimentation rate, CRP: C reactive protein

## Discussion

In this study, we investigated the prevalence of acute pericarditis as a complication in the medical history of 337 CVID patients. We found five patients (1.5%) that had experienced acute pericarditis at different life-times. Here we have reported three of them. One patient (case 1) had experienced three episodes of pericarditis, two of which had happened in the same year; all of these episodes were associated with pneumonia. Positive blood culture for streptococcus pneumonia was reported during the second episode; the exact etiology of pericarditis was not recorded in the patient's files; however, acute pericarditis could occur in children by streptococcus pneumonia, especially with underlying medical conditions such as immune deficiency. There are different opinions about its pathogenesis, as most of the children with pneumococcal pericarditis have positive blood culture for streptococcus pneumonia, which supports the idea of hematogenous dissemination.<sup>11,12</sup> All these patients suffered from concurrent chronic lung disease, mainly sinopulmonary infections and bronchiectasis, and all had pericardial effusion in echocardiography. Pericarditis occurred before the diagnosis of CVID in cases 2 and 3 and also during the first episode of case 1. When the second and third episodes of acute pericarditis occurred in case 1, the patient was not treated with intravenous immunoglobulin (IVIG) for more than 2 months.

Cardiovascular diseases are not common manifestations in CVID.<sup>5</sup> It has been shown that right ventricular dysfunction, cor pulmonale, and pulmonary hypertension can occur in patients with inborn errors of immunity secondary to recurrent respiratory tract infections and bronchiectasis.<sup>6</sup> Johnston et al. reported secondary pulmonary hypertension as a common comorbidity in CVID patients, especially in those who are involved with structural lung diseases.<sup>13</sup> Recently, it has been observed that splenectomy may predispose CVID patients to post-operative pulmonary arterial hypertension; however, it has remained speculative as reported patients also had chronic lung disease.<sup>14</sup>

Autoimmune disorders may be the underlying pathomechanisms for pericarditis in immunodeficient patients, particularly when other more common etiologies are excluded. A case of CVID with giant cell myocarditis

(GCM) was reported for the first time by Laufs et al.,<sup>15</sup> and it was suggested that autoimmunity could be the cause of this inflammatory cardiac manifestation, often occurring in older age group. There is a case report of a 17-year-old Iranian girl with recurrent sinopulmonary infections since the age of 5 years; she was diagnosed with CVID at the age of 14 years. She had complaints of fever and dyspnea while undergoing IVIG treatment. The echocardiography revealed moderate to large pericardial effusion; however, the pathological microscopic assessment and pericardial fluid analysis showed inflammation without any evidence of malignancy and no clinical and laboratory finding was in favor of autoimmunity during 2 years of follow-up.<sup>7</sup>

CVID patients present with diverse clinical manifestations, mostly infectious disorders. Many also face autoimmunity, chronic lung disease, lymphoproliferative disease, gastrointestinal disorder, or malignancy.<sup>16,17</sup> In the current study, the patients presented with numerous infectious and noninfectious complications, including recurrent respiratory tract infections, bronchiectasis, lymphoproliferative disorder, and chronic diarrhea. These inflammatory presentations are the result of immune dysregulation,<sup>16</sup> and acute pericarditis may result for the same reason.

In this retrospective study, we encountered certain limitations, such as not having all clinical and laboratory data and complete treatment profile of every patient because of pericarditis. For more accurate and better propositions, further prospective studies must investigate and evaluate inflammatory heart disease such as pericarditis in CVID patients.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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