Turk Kardiyol Dern Ars 2017;45(7):660-663 doi: 10.5543/tkda.2017.52284

CASE REPORT

A rare complication of chronic granulomatous disease in a child: constrictive aspergillus pericarditis

Bir çocukta kronik granülomatöz hastalığın nadir bir komplikasyonu: Konstriktif aspergillus perikarditi

Emrah Şişli, M.D.,[1] Yasemin Özdemir Şahan, M.D.,[2] Mehmet Fatih Ayık, M.D.,[1] Deniz Nart, M.D.,[3] Yüksel Atay, M.D.[1]

[1]Department of Cardiovascular Surgery, Ege University Faculty of Medicine, İzmir, Turkey
[2]Department of Pediatric Cardiology, Ege University Faculty of Medicine, İzmir, Turkey
[3]Department of Pathology, Ege University Faculty of Medicine, İzmir, Turkey

Summary– A 3-year-old girl with the diagnosis of chronic granulomatous disease (CGD) was hospitalized for bronchopneumonia and congestive heart failure. Her medical history included methylprednisolone medication for autoimmune gastric outlet obstruction. Computed tomography revealed pneumonic infiltrations and pericardial thickening. A pulsed-wave Doppler recording revealed E/A >1. During a pericardiectomy, multiple islands of thick, firm-walled, fibrinous exudate-containing, small abscess formations were observed. Histopathological evaluation of pericardial tissue revealed granulomatous inflammation. Aspergillus fumigatus was cultured from the abscess. In conclusion, development of constrictive aspergillus pericarditis should be considered in patients with CGD because immediate initiation of antifungal management with aggressive surgical treatment is life-saving.

Özet– Kronik granülomatöz hastalık (KGH) tanısı konmuş üç yaşında bir kız çocuğu bronkopnömoni ve konjestif kalp yetersizliği tanıları ile hastaneye yatırıldı. Tıbbi öyküsünde mide çıkım yolunda otoimmün darlık nedeniyle metilprednizolon tedavisi bulunmaktaydı. Bilgisayarlı tomografide pnömonik infiltrasyonlar ve perikart kalınlaşması saptandı. Darbeli-dalga Doppler incelemesinde E/A >1 saptandı. Perikardiyektomi sırasında fibrinöz eksuda içeren çoklu adalar şeklinde, kalın duvarlı apse oluşumları mevcuttu. Perikardın histopatolojik incelemesinde granülomatöz enflamasyon saptandı. Apse'den yapılan kültürde aspergillus fumigatus üredi. Sonuç olarak, KGH'li olan hastalarda konstriktif aspergillus perikarditi dkkate alınmalıdır çünkü beklemeden anti-fungal tedavinin başlanması ile birlikte agresif cerrahi tedavi hayat kurtarıcıdır.

As a primary immunodeficiency, chronic granulomatous disease (CGD) is a rare, inherited disorder caused by reduced nicotinamide adenine dinucleotide phosphate oxidase complex in the phagocytes. Because respiratory burst does not occur, the resulting defective bactericidal activity makes patients with CGD vulnerable to life-threatening infections with Gram-positive bacteria and fungi.[1] Aspergillosis is one of the most common causes of mortality in CGD.[1–3] Among a wide spectrum of dissemination to other organs, pericardial involvement is very rare,[3,4] and usually develops as recurrent pericardial effusions.[2,5]

Presently described is a rare occurrence of aspergillus pericarditis in a constrictive pattern in a child with CGD.

Abbreviations:

CGD *Granulomatous disease*
NYHA *New York Heart Association*

CASE REPORT

A 3-year-old girl with a medical history of homozygous X-linked CGD who was under interferon gamma-1b (1x30 mcg 3 times a week) treatment was admitted to emergency service with fever and shortness of breath. She had been given oral methylpred-

Received: January 30, 2017 *Accepted:* March 20, 2017
Correspondence: Dr. Emrah Şişli. Ege Üniversitesi Tıp Fakültesi, Kalp ve Damar Cerrahisi Anabilim Dalı, İzmir, Turkey.
Tel: +90 232 - 444 13 43 e-mail: dresisli@gmail.com

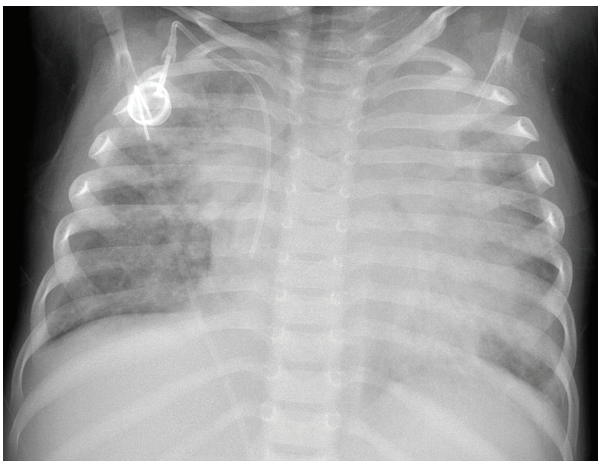

Figure 1. Anteroposterior chest X-ray of the patient revealing bilateral pneumonic infiltrations.

nisolone (20 mg daily) for autoimmune-mediated gastric outlet obstruction, and this treatment had been discontinued 1 month before the current admission. Along with failure to thrive [weight: 11.5 kg (10^{th}-25^{th} percentile); height: 83 cm (<3^{rd} percentile)], physical examination revealed tachycardia (125 beats/minute), tachypnea (70 breaths/minute), fever (38.8ºC), narrow pulse pressure (90/70 mmHg) and distended neck veins with tender hepatomegaly. She was in New York Heart Association (NYHA) class II-III. Peripheral oxygen saturation was 87% in ambient air. Bilateral pneumonic infiltrations were seen on a chest X-ray (Figure 1). Laboratory tests revealed leukocytosis (26.5x103 cells/μL), anemia (hemoglobin: 7.9 gr/dL) and an elevated C-reactive protein level (12.4 mg/dL). Polymerase chain reaction evaluation of viral antigens for respiratory syncytial virus, influenza, parainfluenza, and adenovirus were negative; the exception was coronavirus. Serological assay of galactomannan was positive. Contrast-enhanced computed tomography evaluation of the chest revealed bilateral diffuse lung infiltrates with alveolar condensation, and there was pericardial thickening with abscess formations around the right atrium (24 mm) and at the diaphragmatic surface of the heart (18-32 mm) (Figure 2a, b). She was hospitalized with the diagnosis of pneumonia and congestive heart failure. In addition to an anticongestive regimen, empirical wide-spectrum antibiotherapy with meropenem, linezolid, caspofungin, trimethoprim-sulfamethoxazole, and cymevene was instituted. Trans-thoracic echocardiography revealed no pericardial effusion, but there were hyperechogenic formations at the apex and undersurface of the heart, with approximately 4 to 6 mm of pericardial thickening (Figure 2c). Left ventricular ejection fraction was 65%. There was tethering of the right ventricular free wall with interventricular septal bouncing. A pulsed-wave Doppler recording through the apical window at the tricuspid level revealed inspiratory decrease and expiratory increase in early inflow velocity along with E/A >1 (inspiratory: 1.6; expiratory: 1.9), indicating diastolic dysfunction (Figure 2d). Interferon gamma-1b treatment was continued during the hospitalization period, and she was intermittently given granulocyte-colony stimulating factor.

Through a median sternotomy, the pericardium was dissected free from 1 phrenic nerve to the other until the right ventricle was completely clear and the left ventricle was partially liberated. Of note, there were multiple islands of thick, firm-walled, loculated, fibrinous exudate-containing, small abscess formations (Figure 3a). Soon after the operation, linezolid and meropenem were replaced with piperacillin-tazobactam. A histopathological evaluation of the pericardial tissue revealed intensive granulomatous inflammation, including epithelioid histiocytes, multi-

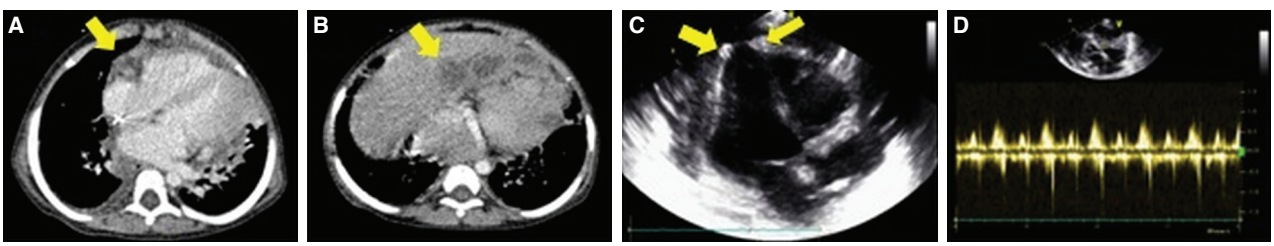

Figure 2. (A, B) Contrast-enhanced computed tomography revealing pericardial thickening and abscess formations adjacent to the right atrioventricular groove and the diaphragmatic surface of the heart. **(C)** Subcostal 4-chamber transthoracic echocardiography denoted hyperechogenic formation around the pericardium. **(D)** Pulsed-wave Doppler recording through the apical window at the tricuspid level revealed inspiratory decrease and expiratory increase in early inflow velocity along with E/A >1.

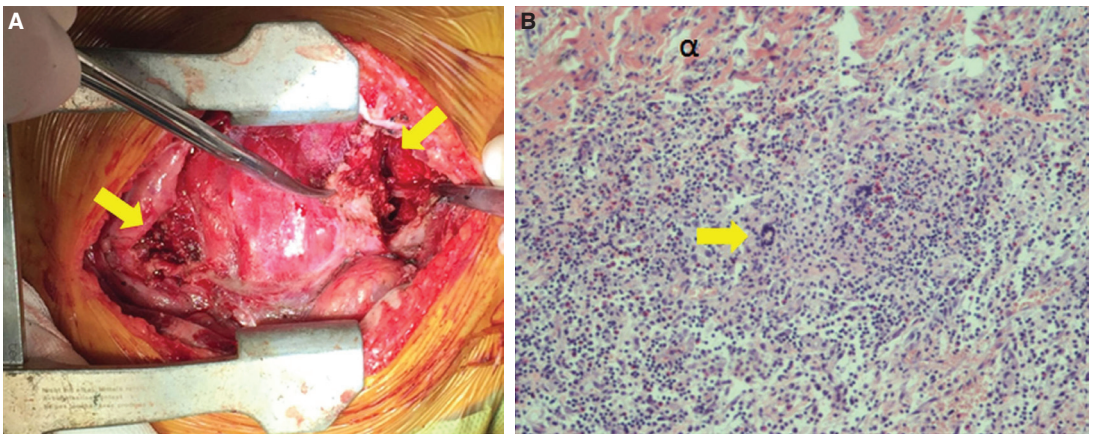

Figure 3. (A) Surgeon's view of the multiple, small, thick-walled, fibrinous exudate-containing abscess formations during pericardiectomy. **(B)** Light microscopy of the pericardium showed pericardial involvement (α) of intensive granulomatous inflammation, including epithelioid histiocytes (arrow), multi-nucleated giant cells, and eosinophilic and lymphocytic infiltration (H&Ex20).

nucleated giant cells, and eosinophilic and lymphocytic infiltration indicating fungal infection (Figure 3b). Aspergillus fumigatus was cultured from the abscess samples, and voriconazole was added to the anti-fungal treatment. In the postoperative course, while she was hemodynamically stable with a remarkable improvement in diastolic function, aspergillus pneumonia necessitated prolonged (12 days) mechanical ventilatory support. In a postoperative pulsed-wave Doppler recording through the tricuspid valve, the E/A was improved (inspiratory: 0.8; expiratory: 1.0) without any change in ejection fraction, which was 62%. Serological assay of galactomannan was positive until 1 month after surgery. The total hospital stay was 2 months, and she was discharged with good hemodynamic condition (NYHA class I). Since that time, she has been under close follow-up for recurrent infection with preemptive treatment of voriconazole (60 mg orally twice a day) and interferon gamma-1b (30 mcg 3 times a week).

DISCUSSION

Pericardial involvement in CGD is very rare,[2,4] and commonly occurs as a result of a contiguous spread from the lung, as in our case.[2] In a review article of invasive aspergillosis among 2121 patients, 37 patients had pericardial involvement, only 3 of whom had CGD as an immune-compromised state.[4] In a retrospective autopsy-based study of the extrapulmonary involvement of invasive aspergillosis among 107 adult patients with hematological malignancy, 30 patients were found to have cardiac involvement, and only 5 involved the pericardium. However, pericardial involvement was not thoroughly examined as to whether it was constrictive or effusive in pattern.[3] Le Moing et al. reported 29 cases with aspergillus pericarditis, of which 3 were of pediatric age and had CGD as an underlying condition. Neither the pediatric cases nor the entire cohort of patients revealed constrictive pericarditis, but rather pericardial effusion.[2]

Patients with CGD are vulnerable to a variety of autoimmune diseases.[6] Pericardial involvement in cases with CGD often presents as recurrent pericardial effusion that is responsive to methylprednisolone medication.[5,6] Although paradoxical to the immune-compromised state of the patients with CGD and the risk of infection, methylprednisolone is recommended in cases with autoimmune conditions.[6] A determined complication of CGD, gastric outlet obstruction, occurred in our patient, but had subsided with methylprednisolone treatment.[1] However, in our opinion and consistent with the literature,[2,4] methylprednisolone medication led to the development of pulmonary aspergillosis, which may have expedited the spread of the aspergillosis to the pericardium in our patient.

In conclusion, aspergillus pericarditis is a very rare and life-threatening condition in patients with CGD. Thus, a high index of suspicion should be maintained in patients with CGD, because early diagnosis with combined medical and aggressive surgical management is life-saving. Additionally, one should be cau-

tious when initiating methylprednisolone medication for autoimmune conditions in patients with CGD.

The case was presented at the 15th National Congress of the Turkish Society of Pediatric Cardiology and Cardiac Surgery (April 13-16, 2016, Antalya, Turkey).

Funding

None declared.

Conflict-of-interest: None declared.

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Keywords: Aspergillosis: chronic granulomatous disease; constrictive pericarditis; pericardiectomy

Anahtar sözcükler: Aspergillosis; Kronik granülomatöz hastalık; konstriktif perikardit; perikardiyektomi.