Chronic pericardial effusion secondary to a influenza virus A (H1N1)/2009 infection

İnfluenza virüs A (H1N1)/2009 enfeksiyonuyla oluşan kronik perikart efüzyonu

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Summary– We report, to our knowledge, the first successful treatment of novel Influenza A (H1N1)/2009 chronic pericardial effusion in an adult. This patient presented on admission respiratory failure and cardiac tamponade which required non invasive ventilation and drainage. Pericardial fluid polymerase chain reaction sequences were positive for Influenza A (H1N1)/2009 virus. Any other etiologies were discarded. Recidivating pericardial effusion after medical treatment, firstly with Oseltamivir, and afterwards, with colchicine and corticosteroids during six months, was solved with pericardiectomy.

Özet– Bilgilerimize göre yeni influenza A (H1N1)/2009 virüsüyle erişkinde oluşan kronik perikart efüzyonunun ilk başarılı tedavisini bildiriyoruz. Bu hasta hastaneye kabul edildiğinde, invaziv olmayan ventilasyon ve drenaj gerektiren solunum yetersizliği ve kalp tamponadı tablosunda idi. Perikart sıvısının bir seri polimeraz zincir reaksiyonu incelemesi influenza A (H1N1)/2009 virüsü için pozitif sonuç verdi. Diğer etyolojiler ekarte edildi. Altı ay boyunca önce oseltamivir, daha sonra kolşisin ve kortikosteroitlerle yapılan tıbbi tedaviden sonra nükseden perikart efüzyonu perikardiyektomiyle iyileşti.

Pericarditis and acute pericardial effusion have been occasionally associated with influenza A infections. Chronic pericardial effusion is an infrequent complication that has not been described in adults but can appear following acute disease. Conservative management is the first-line treatment; however surgery can be used for recurrent effusions or in the event of complications.

Abbreviations:

CEA Carcinoembryonic antigen
ICU Intensive Care Unit
LDH Low-density lipoprotein
PCR Polymerase chain reaction

CASE REPORT

In this case report, we describe a 62-year-old man who presented to our emergency department with respiratory failure and a depressed level of consciousness during an epidemic seasonal flu. He had experienced progressive dyspnea, general malaise, asthenia, and anorexia in the previous six weeks. His medical history was significant for obesity, hypertension, diabetes type 2, and occasional use of tobacco and alcohol. On admission, he had a temperature of 36.5 ºC, blood pressure of 95/60 mmHg, and pulse of 102/minute. Pulsus paradoxicus and jugular venous distention were found on physical examination. He had muffled cardiac sounds with crepitus in the right pulmonary base. His respiratory status was compromised and his oxy-hemoglobin saturation fell below 80%, requiring noninvasive ventilatory support in the Intensive Care Unit (ICU).

Notable abnormal laboratory values included a white blood cell count of 7.500/mL, a creatinine phosphokinase peak level of 71.7 IU/L, a troponin level of 0.03 ng/dL and a myoglobin level of 59 ng/mL. An electrocardiogram showed low voltages, sinus rhythm and re-demonstrated an old right bundle block. A chest radiograph showed diffuse signs of cardiac failure and cardiomegaly. Computed tomography (Fig. 1) and echocardiogram were performed, which demonstrated a normal ventricular size, collapse of the right atrial cavity, moderately compromised pump function (ejection fraction 40%), diffuse hypokinesia and severe pericardial effusion. Ultrasound - guided

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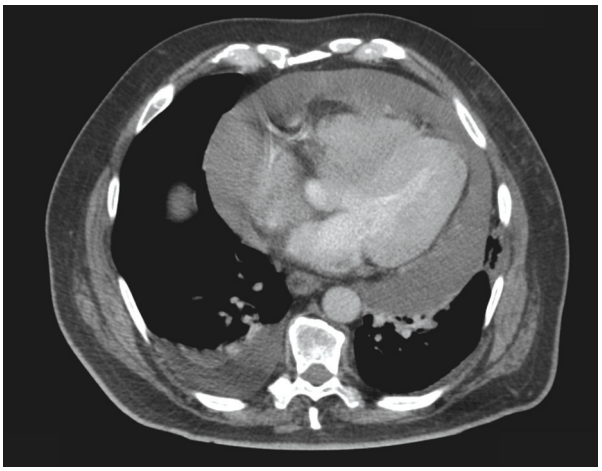

Figure 1. CT scan on admission.

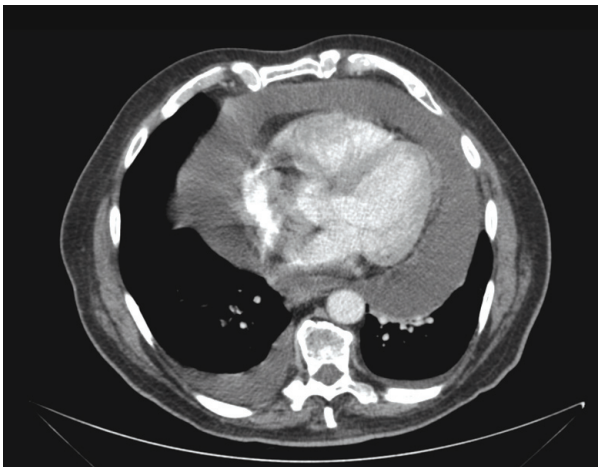

Figure 2. CT scan after 6 months.

pericardiocentesis was performed and yielded 250 cc of light yellow fluid characterized as an exudate. The pericardial low-density lipoprotein (LDH) (113 UI/L) /Serum LDH (180 UI/L) ratio was 0.62, the total pericardial protein (4.9 g/L)/ Serum total protein (6.62 g/L) ratio was 0.74, leukocytes were 180/mm^3 and adenosine deaminase was 13.2 UI/L.

A nasopharyngeal swab sample collected at the Emergency Department was negative for influenza A (H1N1)/2009. Molecular analyses of the pericardial fluid were positive for influenza A (H1N1)/2009 and metapneumovirus A. Sequencing of the amplicons confirmed the results of the pericardial fluid polymerase chain reaction (PCR).

Oral oseltamivir therapy was initiated at a dosage of 75 mg every 12 h for ten days. Tachypnea and cardiac failure gradually improved, and the patient was discharged from the ICU after 5 days.

The patient was also tested for other bacterial (including acid fast bacteria), fungal, and viral respiratory agents in the blood cultures, urine, serum and bronchoalveolar lavage (organisms tested=*Legionella, Streptococcus pneumoniae, Mycoplasma pneumoniae,* rhinovirus, adenovirus, enterovirus, parainfluenza virus and respiratory syncytial virus) and all the results were negative. Multiplex RT-PCR with microarray technology was used to detect respiratory viruses (CLART® Pneumovir, Genómica S.A.U, Coslada, Madrid, Spain, which detects adenovirus, bocavirus, coronavirus type 229, enterovirus (echovirus), influenza virus A H1N1/2009, influenza viruses A, B and C, metapneumovirus A and B, parainfluenza viruses 1, 2, 3, 4a and 4b, rhinovirus, respiratory syncytial virus A and B) in the nasopharyngeal swab and pericardial fluid. Urinary antigen testing for *Legionella pneumophila* serogroup 1 and *Streptococcus pneumoniae* were analysed by immunochromatography (BinaxNOW® Legionella or *S. pneumoniae*, Inverness Medical, Galway, Irland). Testing for acid-fast bacilli was done using sputum bacilloscopy and culture in Löwenstein medium. Serum was tested for *Mycoplasma pneumoniae* IgM (EIA, Vircell, Santa Fé, Granada, Spain). A sputum culture grown in Saboureaud medium was used to test for fungi.

A complete immunological study was performed and the following results were obtained: the globular sedimentation test at 1 hour was 4 mm (normal range [NR]: 0-20); C-reactive protein was 0.88 mg/dl (NR: 0.01-0.5). The anti-streptolysin concentration was <25 UI/mL (NR: 0-200). The lupus anticoagulant tests were negative. Immunoglobulin levels were as follows: immunoglobulin G 905 mg/dl (NR: 768-1632), immunoglobulin A 131 mg/dl (NR: 68-378), immunoglobulin M 31.2 mg/dl (NR: 65-265), immunoglobulin E 14.5 UI/ml (NR: 0-180). CD3+ T-lymphocytes 71% (NR: 65-80%), CD4+ T-lymphocytes 56% (NR: 40-50) and 544.32 mm^3 (NR: 500-800), and CD8+ T-lymphocytes 14% (NR: 26-30) and 136.08 mm^3 (NR: 250-800). B lymphocytes (CD19) 14% (NR: 10-15) and NK cells (CD56) 9% (NR: 5-10). The antinuclear antibody test was negative. The anti- double stranded DNA test was negative. The cANCA level was within normal limits at 3.76 U/mL (NR: 0-20), pANCA was 0.83 U/mL (NR: 0-20). Anticardiolipin IgG antibody was 4.49 U/mL (NR: 0-20) and anticardiolipin IgM

antibody was 2.86 U/mL (NR: 0-10). The rheumatoid factor was <20 UI/mL (NR: 0-33).

Tumor biomarkers were also measured. The carcinoembrionary antigen level was (CEA) 1.42 ng/ml (NR: 0-4.6), alpha fetoprotein was 1.29 ng/ml (NR: 0-6.2), CA-15.3 was 29.83 U/ml (NR: 0-30), CA-125 was 29.09 U/ml (NR: 0-35), and PSA was 0.499 ng/ml (NR: 0-4). Thyroid stimulating hormone (TSH) was 0.82 μU/ml (NR: 0.34-5.6).

The patient was seen again 10.5 months after discharge. There was some remaining chronic pericardial effusion (Fig. 2), asthenia, effort dyspnea, weight loss (22 kilograms) and anorexia. Pericardial drainage was performed when physical disability was present. No infectious etiology was found during follow-up and tumor and inflammatory markers were all negative. Treatment with colchicine (2 mg on the first day, followed by 0.5 mg twice daily for six months) and low doses of corticosteroids (prednisone 0.2 mg/kg/day for six months) were not effective and a pericardiectomy was performed to prevent recurrent effusions.

DISCUSSION

The findings in this case report suggest that the pericardial effusion associated with influenza virus A (H1N1)/2009 infection was caused by direct tropism of the virus.[1] Pericarditis and pericardial effusion have been observed as a complication of influenza A (H1N1) infections in children.[2,3] Cardiac involvement is usually reported to occur between 4 and 9 days after the onset of influenza symptoms and is characterized by worsening dyspnea, electrocardiography abnormalities (i.e., ST elevation and Q waves), elevation of cardiac enzymes, and impaired left ventricular function.[4] In some cases, pericardial effusion may result in cardiac tamponade.[5] Cardiac events generally occur as a clinical consequence of the primary respiratory infection.[6] In our case, cardiac involvement occurred silently or late in the course of the infection. The timing of the cardiac involvement, in combination with detection of the virus in the pericardial fluid, strongly suggests a direct effect of influenza virus A (H1N1)/2009 on the pericardium. Viral tropism for myocardial tissue may be enhanced by the cytokine cascade and by enhancing or modifying viral receptors on the endothelial cells lining the myocardial tissue. Immune-mediated pathology in the case of infectious pericarditis has been suspected[7] but in our patient, the immunology study suggested a chronic state of inflammation.

Our case report demonstrates that pericardial effusion may occur as a result of infection with influenzavirus A (H1N1)/2009. Puzelli et al.[8] suggest that influenza virus A (H1N1)/2009 is more commonly associated with severe forms of cardiac involvement than the other circulating influenza virus strains. There are no reports that show that metapneumonvirus A has pathogenic effects on the pericardium but infection with this virus may potentiate co-existing cardiac disease.

A hypothesis for the negative nasopharyngeal swab for influenza virus A (H1N1)/2009 and the positive influenza virus A (H1N1)/2009 PCR testing in the pericardial liquid could be that this virus remains latent in the pericardial fluid after other clinical features of viral infection have resolved or improved. The absence of high C-reactive protein levels or other markers of acute inflammation could be explained by the study by Pankuweit et al.,[9] in which autoreactive pericarditis led to an elevation of cytokines (interleukin 6 and 8) and interferon gamma that was only detected in the pericardial fluid but not in sera. Although influenza virus A (H1N1)/2009 rarely leads to cardiac complications, pericardial effusion and other severe cardiac events need to be considered when this virus is suspected.

Furthermore, the above data strongly highlights the importance of early diagnosis and treatment. If medical treatment fails to be effective, surgical pericardiectomy may be an effective alternative.

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Key words: Heart/virology; heart failure/diagnosis; influenza A Virus, H1N1 subtype/isolation & purification; influenza, human/complications; pericardial effusion/virology; pericarditis.

Anahtar sözcükler: Kalp/viroloji; kalp yetersizliği/tanı; influenza A virüs, H1N1 alt tipi/izolasyon ve arındırma; influenza, insan/komplikasyonlar; perikart efüzyonu/viroloji; perikardit.