Eisenmenger syndrome and juvenile rheumatoid arthritis – a case of double diagnosis

Współistnienie zespołu Eisenmengera i młodzieńczego zapalenia stawów – opis przypadku

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Abstract

An 8.5-year-old girl evaluated for central cyanosis, hypoxia and normocarbia was found to have aorticopulmonary window and pulmonary hypertension. The diagnosis of Eisenmenger syndrome (ES) was made and treatment with bosentan was started. Four months later she was diagnosed to have juvenile rheumatoid arthritis and naproxen treatment was started. The case was remarkable in that she showed clinical improvement with new generation treatment of ES although pulmonary arterial pressure did not decrease significantly and the diagnosis of juvenile rheumatoid arthritis was made during follow-up.

Key words: bosentan, Eisenmenger syndrome, juvenile rheumatoid arthritis, pulmonary arterial hypertension

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Introduction

Eisenmenger syndrome (ES) is defined as an irreversible increase in pulmonary vascular resistance and characterised by right to left shunt in the connection point of the pulmonary and systemic circulation [1]. Juvenile rheumatoid arthritis (JRA) is characterised by chronic synovitis and associated extra-articular findings [2]. In the literature, the association of JRA and ES has not been previously reported. Here we report a paediatric case with ES who showed clinical improvement with new generation treatment of ES and was diagnosed to have juvenile rheumatoid arthritis during follow-up.

Case report

A girl aged 8.5 years was referred to our hospital with the complaints of cough, dyspnoea, chest pain and fatigue for the last month. She had been followed with a diagnosis of mitral insufficiency and heart failure between the ages of 6 months and 3 years in another centre. She was excluded from the follow-up at the age of 3 years because of clinical and echocardiographic improvement.

During the month before her admission, she was treated with large spectrum antibiotics with the diagnosis of pneumonia. On her admission to our hospital, she had a pulse of 120/min, respiratory rate of 44/min, oxygen saturation of 60-77%. Her physical examination revealed perioral cyanosis, clubbing in the thumbs, hyperdynamic apex, systolic murmur of II/VI at the left lower border of the sternum and hepatomegaly. Mild right axis deviation (+100°) and R/S ratio of 1 in V_1 in electrocardiogram (Figure 1), prominent pulmonary conus and proximal pulmonary arteries in chest radiogram (Figure 2) were found. Thorax computerised tomography was normal. Echocardiographic examination revealed that the right atrium and the right ventricle were slightly larger than the left chambers. The interventricular septum was slightly deviated to the left. Persistent cyanosis and normal CO_2 pressure in spite of hypoxia in arterial blood gases analysis suggested a pathological cardiac condition.

Cardiac catheterisation showed right ventricular pressure of 110/0-10 mmHg, pulmonary arterial pressure of 99/72 (mean 83) and aortic pressure of 97/72 (mean 83) mmHg. Pulmonary vascular resistance was 31.4 Woods

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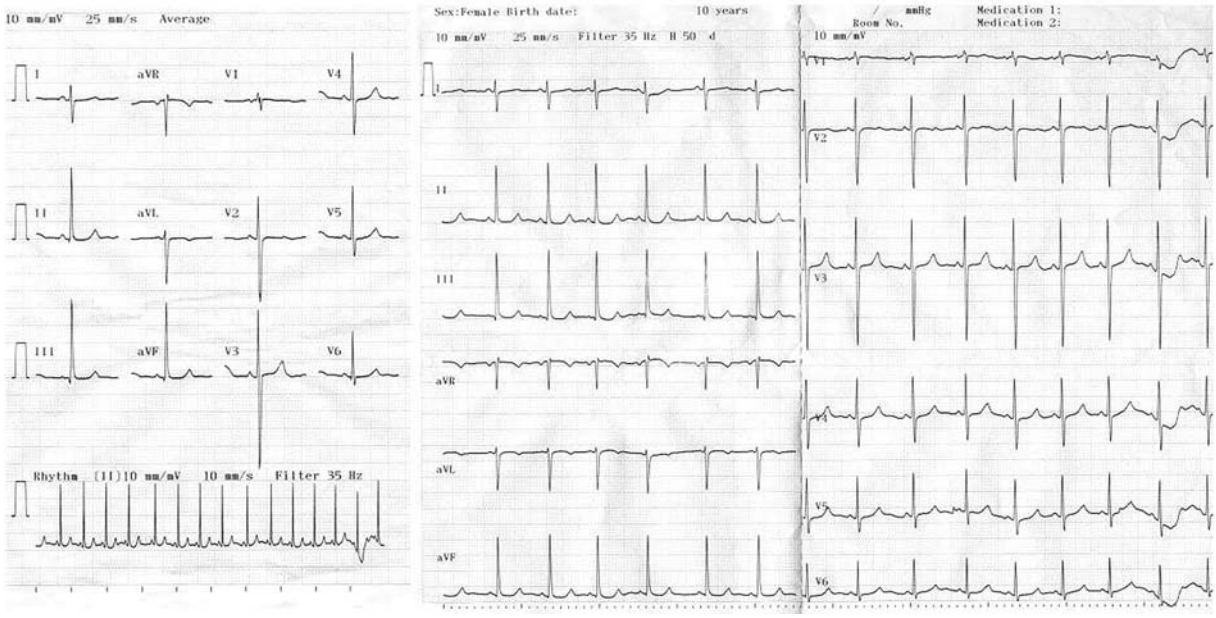

Figure 1. ECG shows right axis deviation and R/S = 1 in V_1

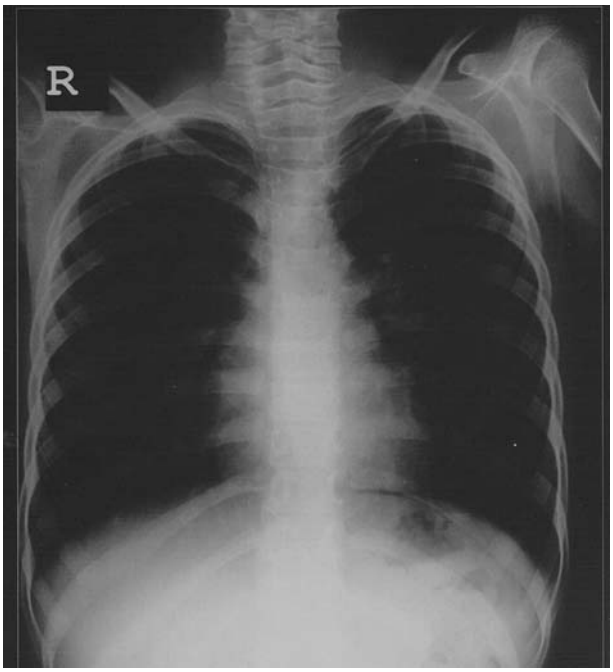

Figure 2. Prominent pulmonary conus and proximal pulmonary arteries in chest radiogram

units/m^2 and the ratio of pulmonary vascular resistance to systemic vascular resistance was 0.63. Acute vasoreactivity test performed by intravenous iloprost did not show a decrease in pulmonary arterial pressure. An aorticopulmonary window (APW) causing two-directional shunt at the level of the ascending aorta was determined. The patient was diagnosed to have APW and ES.

Before the start of treatment the 6-minute walking test was performed [3-5]. The patient was able to walk only for 1.5 min and covered a distance of 45 m. The test was ended because of aggravation of cyanosis and decrease in oxygen saturation from 65% to 57%. Bosentan (2 × 31.25 mg) treatment was started, together with chronic digoxin and enalapril treatment. The patient was discharged. Bosentan dose was increased to 2 × 62.5 mg at the end of the first month. At the end of the third month of bosentan treatment her oxygen saturation increased to 80% and functional capacity was improved from class IV to class III according to the World Health Organization (WHO) classification [3]. She was able to walk 270 m during the 6-minute walking test and no decrease in oxygen saturation was observed at the end of the test. She was also included in the heart-lung transplantation waiting list of the Ministry of Health of Turkey.

During the 4th month of treatment, she started to complain of swelling and pain in the right knee. Her medical history was reviewed in detail and it was learnt that she had made similar complaints of pain and swelling in the knees since the age of 4 years and she had undergone several diagnostic knee punctures. However, no definite diagnosis was made. She did not have associated complaints such as fever, rash or other joint findings. Physical examination of the patient revealed swelling, warmness and limitation of motion in the right knee. Laboratory examination showed haemoglobin of 14.6 g/dl, leukocyte count of 13 100/mm^3, erythrocyte sedimentation rate (ESR) of 21 mm/h, C-reactive protein (CRP) of 9.1 mg/dl (0-0.8 mg/dl), fibrinogen of 553 mg/dl, rheumatoid factor negative, urea of 20 mg/dl, creatinine of 0.6 mg/dl, aspartate transaminase (AST) of 21 IU/l, alanine aminotransferase (ALT) of 11 IU/l. In addition, antinuclear antibody (ANA), anti-deoxyribonucleic acid

(anti-DNA) antibody, Salmonella serology and mutation analysis for familial Mediterranean fever were found to be negative. Ophthalmologic examination demonstrated iridocyclitis. Thus, the patient was diagnosed to have JRA and treatment with oral naproxen (2 × 150 mg) was started. After one month of treatment symptoms improved. Her ESR was 2 mm/h, CRP was 0.1 mg/dl and fibrinogen was 411 mg/dl. She is still on naproxen treatment and symptom free at 18 months of follow-up.

She has been followed up with 6-minute walking tests performed every 3 months. At the 18th month of follow up, she was able to walk 350 m, oxygen saturation was 83% and her functional capacity was class II. No side effects of bosentan were observed and transaminase levels remained within normal limits. She underwent cardiac catheterisation which demonstrated right ventricular pressure of 105/0-2 mmHg, pulmonary arterial pressure of 103/69 (mean 85) mmHg and aortic pressure of 100/70 (mean 83). Pulmonary vascular resistance was 28.4 Woods units/m^2 and ratio of pulmonary vascular resistance to systemic vascular resistance was 0.79.

Discussion

Aorticopulmonary window is a rare congenital heart disease, which is a defect in the septum between the aorta and the pulmonary artery. Half of these conditions are associated with complex heart diseases. Aorticopulmonary window is a result of incomplete separation of the truncus arteriosus and incomplete development of the septum between the aorta and the pulmonary artery. This condition may be fatal in untreated cases due to rapid development of pulmonary hypertension (PH) [4].

Pulmonary hypertension is defined as pulmonary arterial pressure higher than 25 mmHg at rest and 30 mmHg during exercise [3, 4]. Stretch in the pulmonary arterial wall and endothelial injury cause secretion of mediators, which results in vasoconstriction, thickening of the arterial wall and development of thrombus. As a result, pulmonary artery diameter decreases and pulmonary vascular resistance increases, resulting in PH [1]. The most recent classification of PH was made in 2003 [5]. In this classification, group 1 PH includes pulmonary arterial hypertension while groups 2-5 include PH secondary to various conditions [5]. According to this classification, our patient, who has PH associated with systemic-pulmonary shunts, is included in PH group 1.

Eisenmenger syndrome can be seen in association with many congenital heart diseases. This condition can manifest as the reversal of shunt present at the pulmonary or aortopulmonary level and development of irreversible PH. Eisenmenger syndrome presents in infancy if it develops at the aortopulmonary level and has a higher mortality rate [4]. Less frequently, symptoms may develop later in life, as in our case.

In our case, symptoms of heart failure started in infancy, but APW diagnosis could not be established at this age. She was excluded from the follow-up since heart failure symptoms were improved by treatment at the age of 3 years and the treatment was stopped. She was free of symptoms until the last month before admission, probably because of her self-limitation of physical activity. However, persistence of complaints and cyanosis after a lower respiratory tract infection led to referral to our hospital. Following her admission, her cyanosis seemed to start suddenly. She was evaluated for lower respiratory tract diseases and they were excluded from the differential diagnosis. Although her cyanosis persisted, echocardiographic examination did not reveal any explanatory finding. Since arterial blood gases analysis showed normal CO_2 with hypoxia, cardiac catheterisation was performed and revealed PH. The diagnosis of APW was made.

The result of the acute vasoreactivity test is a determinant in the treatment of pulmonary hypertension and the first choice is the use of vasodilator drugs [3, 4]. This test is performed with inhaled nitric oxide, intravenous epoprostenol or iloprost. The test is accepted to be positive in the following conditions: pulmonary arterial pressure decreases more than 20% (approximately 40 mmHg); no change is observed in the ratio of pulmonary vascular resistance to systemic vascular resistance; or there is a decrease in this ratio with normal right atrial pressure and cardiac output. [4]. Calcium channel blockers should be started in children with pulmonary hypertension and positive vasoreactivity test. If the test is negative new generation pulmonary vasodilator drugs such as prostanoids, phosphodiesterase-5 inhibitors and endothelin receptor antagonists can be used. In cases with a negative vasodilator response, with no heart failure and with functional capacity of III or IV according to WHO classification, the first choice of treatment can be endothelin receptor antagonists [3-8]. If this treatment fails, combination therapies can be considered [3].

At the time of diagnosis of ES and APW, the functional capacity of our patient was class IV and the acute vasoreactivity test was negative. That is why the treatment with bosentan, which is a blocker of both endothelin receptors, was started. It has been demonstrated that bosentan increases the walking distance in the 6-minute walking test, improves haemodynamic parameters and quality of life by vasodilatation and decreases collagen production [9]. Although the experience with bosentan in children with ES is limited, we started bosentan in our patient [6-8]. The effectiveness of the drug can be best evaluated after 3 months of treatment. We observed improvement in walking distance, increase in oxygen saturation during physical activity and improvement in quality of life. However, it has been reported that improvement with bosentan treatment may not persist longer than one year [7, 8]. As a result, these patients

needed combined treatments or they died [6-8]. In contrast to these reports, in our patient no side effects of bosentan have been observed during 18 months of treatment and there was a significant improvement in clinical findings and walking distance in the 6-minute walking test. Most remarkably, her walking distance increased to 380 m, which has prognostic value, and her functional capacity was stabilised at class II [3]. However, her recent cardiac catheterisation did not show significant improvement in pulmonary artery pressure and other measurements. Since the main target of treatment in this group of patients is to improve the quality of life, the results of cardiac catheterisation could be ignored. In addition, the response to treatment may be limited and our patient has been included in the heart-lung transplantation waiting list as a last option of treatment [4].

Juvenile rheumatoid arthritis can be classified according to the number of involved joints, fever and rash as pauciarticular JRA (type I and II), polyarticular JRA or systemic JRA [2]. Since our patient had complaints concerning both knees for 4.5 years with no associated fever or rash, she was diagnosed to have pauciarticular JRA type I. Pauciarticular JRA type I is the most common type of JRA in children, is more frequent in girls, and usually presents in early childhood. It usually involves large joints. Chronic iridocyclitis is an associated finding in 30% of cases and rheumatoid factor is usually negative [2]. In our case, age of onset, sex, large joint involvement, association with iridocyclitis and negative rheumatoid factor all suggested the diagnosis of pauciarticular JRA type I. However, ANA, which is positive in 90% of pauciarticular JRA patients, was negative in our patient. After one month of naproxen treatment, the joint complaints of our patient improved and acute phase reactants were found to be negative. She was symptom free for her 18 months of follow-up with a good response to treatment.

A review of the literature revealed no previous reports of ES and JRA association. Our case is considered to be interesting in that sense. Survival of children with PH has been improved in recent years with the understanding of pulmonary vascularisation and development of new treatment options [4]. Our case shows that bosentan is a treatment of choice, improving quality of life in children with ES.

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