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Right atrial myxoma in a patient with systemic sclerosis: a paraneoplastic syndrome or the coexistence of two diseases connected to increase in interleukin 6

Śluzak prawego przedsionka u pacjenta z twardziną układową — zespół paranowotworowy lub współwystępowanie dwóch chorób związane ze zwiększeniem stężenia interleukiny 6

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Abstract

The myxoma makes 80–90% of benign cardiac neoplasms. The first symptom in 50% of patients is an embolism resulting from relocation of tumor fragments or blood clots into the bloodstream. Elevated values of acute phase proteins in these patients are results of non-specific immune response to an antigen causing the disease. Interleukin 6 (IL-6) plays a role in this reaction, modifying inflammatory response by: influence on lymphocyte T differentiation, lymphocyte B to plasmocyte transformation, and stimulation of the liver to produce acute phase proteins. Elevated IL-6 is found in 80% of patients with diagnosed myxoma, which causes it to be an important marker in diagnostic and post-operational monitoring. The role in non-specific inflammatory response played by IL-6 in myxoma and autoimmune disorders was a cause of many diagnostic mistakes. Available literature does not suggest a coincidence of cardiac myxoma and systemic sclerosis. This is why we would like to present a case report, with special regard to correlation between IL-6 values and activity/stage of diagnosed disorders.

Key words: myxoma, interleukin 6

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Introduction

Primary cardiac tumors can be benign or malignant. The incidence is estimated at 0.0017–0.28% of general count of all neoplasms [1]. Myxoma is diagnosed in 80–90% of all cases of benign cardiac tumors [2]. In approximately 75% it is localized in the left atrium, in 18% in the right atrium, in 4% in right ventricle, in 3% in left ventricle and sporadically on leaflets of the valves [3, 4]. The neoplasm can occur at any age, but it is diagnosed most frequently between 30th and 60th year of age [5, 6]. Additional symptoms that accompany myxoma are non-characteristic and include loss of body mass, elevated body temperature, skin changes, joint and muscle aches and others, caused by presence of tumor in the cavities of heart [6, 7]. Additional investigations often show elevation of acute-phase proteins,

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immunoglobulins, anti-nuclear antibodies (ANA) and rheumatoid factor (RF). The abovementioned symptoms and laboratory results are called the myxoma syndrome [6]. Cardiovascular symptoms are caused by inappropriate working of the heart due to tumor mass or vascular complications caused by displaced tumor fragment. Left atrial localization results in obstruction of blood flow into ventricles, which causes symptoms typical for aortic stenosis or — rarely — for its insufficiency. Acute left ventricular insufficiency or sudden loss of consciousness may be the first symptoms of the tumor.

Embolisms that happen in about 50% of patients may often be one of the first symptoms of myxoma, and are caused by displacement of the tumor fragments or embolisms from the surface of the tumor into vascular system. Localization of embolisms depends from localization of the tumor or intracardiac connections. Myxomas of left ventricle or left atrium cause systemic embolisms often localized in the central retinal artery or nervous system When localized in either right ventricle or right atrium, this neoplasm may cause pulmonary embolisms [7].

General symptoms and the presence of acute-phase proteins are characteristic of inflammatory diseases, including those with autoimmunological background such as systemic diseases of connective tissue. They all are result of immune response to an antigen that is causing the disease in which interleukin 6 (IL-6) plays an important role. IL-6 is a cytokine that modifies immune response through: the influence on lymphocyte T differentiation, lymphocyte B transformation and liver stimulation to produce acute-phase proteins. Hirano et al. have discovered that myxoma cells produce IL-6, which may be largely responsible for the myxoma syndrome [8]. Increased levels of this cytokine can be found in 80% of patients with confirmed diagnosis [7]. Interleukin 6 is at present a very important marker for diagnosing myxoma and monitoring after operation. Additionally, a correlation between systemic sclerosis, especially of the type complicated by interstitial lung disease, and concentration of IL-6 has been proven [9, 10]. The participation of IL-6 in non-specific immune response in myxoma and autoimmune diseases has been the cause of diagnostic errors. There have been situations where myxomas have been primarily diagnosed as rheumatoid disorders [6, 9, 11, 12]. Based on available literature, we can conclude that the coexistence of systemic sclerosis and myxoma has not been previously described. This is the reason why we present the case of a patient with systemic sclerosis and asymptomatic right atrial myxoma, with special attention paid to connection between IL-6 and activity of abovementioned disorders.

Case report

A 55-year-old, previously healthy male was admitted to the Department of Rheumatology and Internal Diseases PUM with suspicion of systemic sclerosis. He complained of skin hardening and thickening on the face, neck, chest, forearms, hands, thimble-like scars and ulcers of fingertips, skin discoloration, Raynaud symptom, decrease tolerance to physical exertion, chest pains not related to exercise, heartburn, and body mass loss. There was a silent diastolic heart murmur in Erb's point.

Laboratory examinations revealed: ESR increased to 28 mm/h, reticulocytosis 56‰, microalbuminuria — 0.65 mg/l, increased concentration of creatinine phosphokinase — 338 U/L. Conducted serological examinations have shown the presence of anti-nuclear antibodies (ANA) of 1:2560 titer with speckled staining pattern. Other antibodies like anti-centromere (ACA), anti-topoisomerase-I (Scl-70), anti-endothelial cells (AECA), granulocyte cytoplasm (ANCA) and anti-cardiolipin antibodies as well as krioglobulin and immunological complexes were not found.

Esophageal scintigraphy have revealed peristalsis disturbance, and gastroduodenoscopy have shown an esophageal inflammation. High definition computed tomography (HDCT) revealed interstitial lung disease.

Based on clinical symptoms and additional examinations, a systemic scleroderma with large areas of the skin being affected was diagnosed. Esophagus and lungs also were affected. Diagnosis was established according to American Rheumatology Association (ARA) criteria. Cyclophosphamide in doses of 600 mg/m^2 administered in 30 day intervals during first 6 months of therapy, and every other month in the next 18 months of therapy. At present, the patient is receiving cyclophosphamide in this dose every third month.

During the first hospitalization after 1st dose of cyclophosphamide was administered, the patient underwent an echocardiography as a routine examination, which revealed the tumor of the right atrium to be 33 mm × 51 mm in size, pedunculated by interatrial septum, movable, and of diversified structure (Figure 1). Due to urgent need of operation, a coronary angiography was conducted the same day. Significant stenoses of proximal segment of the left anterior descending artery and proximal segment of the second marginal branch were found.

The patient underwent an operation to remove the atrial tumor and to implant coronary artery bypass graft. Histopathological examination revealed a myxoma.

The concentration of IL-6 was measured in this patient prior to the operation, and was monitored afterwards. Pre-operational cytokine concentration reached 11.7 pg/ml,

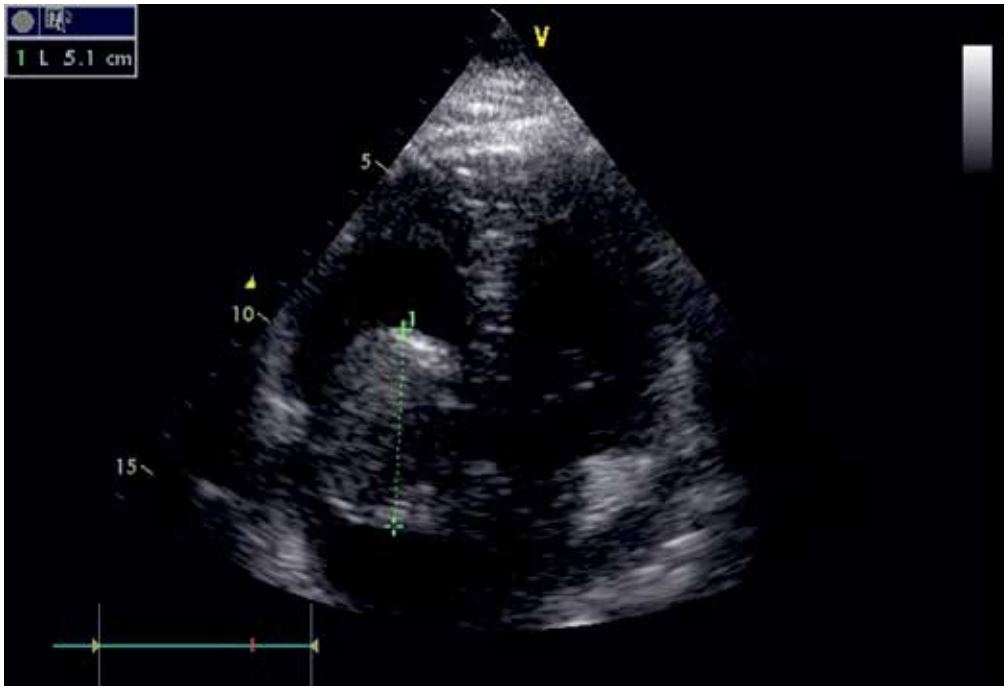

Figure 1. The echocardiographic 2D four-chamber apical projection, which showed the tumor of the right atrium 33 mm × 51 mm in size, pedunculated by interatrial septum, movable, and of diversified structure

being nearly five times greater than reference value, which should be below 2.5 pg/ml. After 1 month from operation, IL-concentration decreased nearly by a half, reaching 6.9 pg/ml, and 4 months later this value was 3.0 pg/ml. Echocardiography did not show any recurrence of the tumor. Presently, the patient is regularly monitored by a cardiologist and a rheumatologist; he also underwent a proper rehabilitation therapy and returned to good physical condition.

Discussion

In presented case a myxoma of the right atrium was revealed during routine diagnostics of the cardiovascular system of the patient suffering from systemic scleroderma. The tumor was asymptomatic. IL-6 concentration before operation was considerably elevated, and was systematically decreasing after tumor removal, having never reached the appropriate values.

The systemic symptoms due to immunological response, which are accompanied by IL-6 elevation in case of myxoma, have been misleading in the past. There have been cases described, where myxoma was primarily diagnosed as systemic lupus erythematosus, polymyositis, antiphospholipid syndrome or systemic vasculitis [7, 9, 11, 12]. After the removal of the tumor all changes connected with immunological response were alleviated, and the IL-6 levels normalized. To our best knowledge, a case of coincidence of systemic scleroderma and myxoma has not been described in literature.

In systemic scleroderma, an important role in vascular damage, especially the beginnings of fibrosis process, is given to cytokines: IL-2, IL-6, and TNF-alfa. Lymphocytes are the source of those cytokines, and IL-6 sources are lymphocytes Th2, and other non-immunological cells including fibroblasts. Needleman et al. have proven that fibroblasts in systemic scleroderma produce 30 times more IL-6 than fibroblasts from control group [13]. It has also been proven that the concentration of IL-6 is connected with the activity of systemic scleroderma and acts as a prognostic factor for organ lesions, especially those occurring in the lungs [10, 14]. Similar to our patient, individuals having large areas of the skin affected are more likely to have IL-6 levels increased. Despite a decrease in IL-6 values in our patient, systemic scleroderma symptoms were still present, but with lesser intensity.

The question is: Whether the systemic scleroderma symptoms were caused by two coincidental diseases or were connected by a chain of etiopthogenetic events? Myxoma produces IL-6, which is crucial in the pathogenesis of scleroderma. It is also important to ask whether scleroderma symptoms are a paraneoplastic syndrome in case of myxoma.

Conflict of interest

None.

Streszczenie

Śluzak stanowi 80–90% łagodnych nowotworów serca. U 50% pacjentów objawia się zatorowością związaną z uwalnianiem się jego fragmentów do krwiobiegu. Podwyższone wartości białek ostrej fazy u tych pacjentów są rezultatem niespecyficznej odpowiedzi układu odpornościowego na antygen nowotworu. Interleukina 6 (IL-6) odgrywa rolę w tej odpowiedzi, modyfikując reakcję zapalną poprzez wpływ na różnicowanie się limfocytów T, transformację limfocytów B w plazmocyty i stymulację wątroby do produkcji białek ostrej fazy. Podwyższone stężenia IL-6 obserwuje się u 80% pacjentów z rozpoznanym śluzakiem, co czyni ją ważnym markerem w diagnostyce i monitorowaniu pooperacyjnych nawrotów guza. Rola, jaką IL-6 odgrywa w śluzaku i chorobach o podłożu autoimmunologicznym, była przyczyną częstych pomyłek diagnostycznych. Dlatego autorzy prezentują przypadek ze szczególnym uwzględnieniem korelacji między wartościami IL-6 a aktywnością i zaawansowaniem współistniejących chorób.

Słowa kluczowe: śluzak, interleukina 6

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References

1. Roberts W.C. Primary and secondary neoplasms of the heart. Am. J. Cardiol. 1997; 80: 671–682.
2. Perchinsky M.J., Lichtenstein S.V., Tyers G.F. Primary cardiac tumors: forty years' experience with 71 patients. Cancer 1997; 79: 1809––1815.
3. Sabatine M., Colucci W., Schoen F. Primary tumors of the heart. In: Braunwald E., Libby P., Zipes D., Bonow R.O. (eds.). Braunwald's heart disease. 7th ed. Elsevier Masson, Philadelphia 2005.
4. Jedliński I., Jamrozek-Jedlińska M., Bugajski P. et al. Asymptomatic myxoma of the tricuspid valve septal leaflet. Kardiol. Pol. 2012; 70: 609–611.
5. Reynen K. Frequency of primary tumors of the heart. Am. J. Cardiol. 1996; 77: 107.
6. Hövels-Gürich H.H., Seghaye M.C., Amo-Takyi B.K. et al. Cardiac myxoma in a 6-year-old child — constitutional symptoms mimicking rheumatic disease and the role of interleukin-6. Acta Paediatr. 1999; 88: 786–788.
7. Byrd W.E., Matthews O.P., Hunt R.E. Left atrial myxoma presenting as a systemic vasculitis. Arthritis Rheum. 1980; 23: 240–243.
8. Kanda T., Umeyama S., Sasaki A. et al. Interleukin-6 and cardiac myxoma. Am. J. Cardiol. 1994; 74: 965–967.
9. Jakóbisiak M. (ed.). Immunology. PWN, Warsaw 1998.
10. Lis A., Brzezińska-Wcisło L. Serum interleukin-6 and 2 levels as a markers of scleroderma progress. Pol. Merk. Lek. 2001; 11: 206–209.
11. Fitzpatrick A.P., Lanham J.G., Doyle D.V. Cardiac tumors simulating collagen vascular disease. Br. Heart J. 1986; 55: 592–595.
12. Elikowski W., Pawelczyk K., Bielski K. Left atrial myxoma mimicking connective tissue disease. Wiad. Lek. 1992; 21–22: 847–848.
13. Needleman B.W., Wigley F.M., Stair R.W. Interleukin-1, interleukin-2, interleukin-4, interleukin-6, tumor necrosis factor alpha, and interferon-gamma levels in sera from patients with scleroderma. Arthritis Rheum. 1992; 35: 67–72.
14. Stuart R.A., Littlewood A.J., Maddison P.J., Hall N.D. Elevated serum interleukin-6 levels associated with active disease in systemic connective tissue disorders. Clin. Exp. Rheumatol. 1995; 13: 17–22.