CLINICAL CASE

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EBV-INFECTION ASSOCIATED NON-EFFUSIVE PERICARDITIS: TWO CASE REPORTS

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Summary. *Two cases of non-effusive pericarditis associated with serologically proven Epstein – Barr virus were reported. Almost healthy young males had complaints of abrupt onset of retrosternal chest pain that appeared during breathing or moving. Other common causes of chest pain must be ruled out, including cardiac ischemia, pneumonia, costochondritis, pulmonary embolism and substance abuse (cocaine). The past medical history were unremarkable, they denies recent use of medications. During physical exanimation a pericardial friction rub was not heard, X-ray was normal. The 2015 updated European Society of Cardiologists Guidelines for the diagnosis and management of pericardial diseases recommended ECG, Echo, measurement of inflammatory or myocardial injury markers. The presentation and discussion of ECG typical changes and Echo signs that proved diagnosis of acute pericarditis were reported. Potential causes of pericarditis are numerous and include trauma, viral infection, tuberculosis, malignant disease and autoimmune conditions. The search for causative factors is often fruitless, because the condition is deemed to be idiopathic. It is common that viruses can lead to acute pericarditis, but only few cases of EBV-associated pericarditis have been previously published. Broad serological tests of infectious diseases were taken. EBV-associated effusive or non-effusive pericarditis may develop without any signs of the infectious mononucleosis in young and almost healthy patients. Both patients made a good physical recovery after being placed on special non-steroid anti-inflammatory drugs, colchicine therapy.*

Key words*: acute pericarditis, Epstein – Barr virus, ECG changes, transthoracic Echo, NSAID.*

Case 1

A 26-year-old Caucasian man had a four days history of acute retrosternal chest pain associated with chills, fever and sore throat. He had had no previous medical history and hadn't been on any medications. On the day of admission to the hospital he developed nausea, vomiting and diarrhea, associated with extreme headache, tiredness and weakness. The chest pain had the patient to sitting forward and was extremely severe, so he hadn't been able sleep for several nights, even to breathe that worse on inspiration.

His physical examination revealed several abnormalities: patient was in acute distress, sweating, had red vascular injected conjunctivas, his throat was erythematous, tonsils were enlarged and exudative, containing purulence, right retro-auricular region was painful to palpation, body temperature was 37, 2 °C; lungs were almost clear to auscultation and percussion, only soft rub in the lower left parasternal area was suspected. During cardiovascular system examination borders of the absolute and relative heart dullness were slightly extended, fine cardiac tones without additional murmurs were auscultated, mild tachycardia presented, BP was 120/80 mm Hg; respiratory rate was 20 breaths per minute, SpO2 = 95% were detected. Heart sounds were normal with no evidence of pericardial friction rub. Abdomen was soft, distended, flat, with hyperactive typical gargling bowel sounds, negative Blumberg sign. No hepatomegaly or uncle edema were discovered.

It was necessary to exclude various disorders as acute pneumonia, pleural reactive involvement, myositis, ischemic heart disease, acute pericarditis, acute pancreatitis, acute gastric ulcer and acute gastroenterocolitis. Radiographs of the chest and ultrasound examination of the abdomen were normal, gastroscopy revealed the presence of duodenogastral reflux only. On the ECG sinus tachycardia,

102 beats per minute, diffuse myocardium changes were observed (Fig.1). Transthoracic Echo revealed no structural abnormalities, with good contractility of myocardium and normal amount of pericardial fluid, E‹A, and thickening of the pericardium layers in the posterior – basal area up to 4 mm (normal thickness less than ‹2 mm) [1]. Laboratory investigations, such as cell blood count (CBC), urinalysis, a routine biochemical profile and coagulation tests were almost normal: with except an acceleration for an erythrocyte sedimentation rate (ESR) - 21 mm/hour. The preliminary diagnosis of acute pericarditis included serological evaluations, blood culture analysis, and polymerase – chain reaction (PCR). Blood culture was sterile. An immunology test and PCR revealed reactivation of the latent EBV infection (positive EBV VCA IgG and EBV EBNA IgG). PCR was also positive for EBV DNA. The patient was treated for 7 days with IV ceftriaxone (2 g q 24 hours), azythromycin 500 mg, diclofenac 75 mg, dexamethazone 4 mg, colchicine 0,5 mg, omeprazole 20 mg, bisoprolol 2,5 mg, acetylsalicylic acid (ASA) 100 mg, spasmolitics. As a result, his condition improved. After one month without complaints ECG revealed several pathological changes as negative T-waves on the V4-V6 leads (Fig.2), no changes in Echo data. Patient was recommended to continue ASA 75 mg twice per day and small doses of в-blocker; two months later no ECG changes was confirmed.

Case 2

A 35–year–old Asian man was admitted to the hospital with complaints of a sore throat, discomfort in the chest like atypical pain, associated with chills and fever. The pain in the chest rose while moving or changing of the body position and most of the time patient was sitting bent forward. Patient was ill-appearing, in no acute distress; his conjunctivas and throat were clear, and tonsils were not enlarged. No lymphadenopathy and thyriodmegaly were discovered. The case considered as upper respiratory tract infection (URI). Cardiovascular system examination revealed non-extended borders of the absolute and relative heart dullness, but soft rub in the lower left parasternal area was suspected. Mild tachycardia was the only abnormality observed on physical examination: cardiac tones without murmur or S3/S4 gallop, pulse was weak, BP = 110/60 mm Hg; SpO2 = 95 %. Nothing special abdomen abnormalities were detected.

As for the suspicion of the URI, an X-ray examination was provided and no pathological changes were observed. The results of patient's blood analysis were as follows: C-reactive protein level (88,79) mg/l and erythrocyte sedimentation rate were elevated; however, the troponin and creatinine kinase levels were within normal limits.

ECG demonstrated regular sinus rhythm, ST elevation up to 1-1,5 mm in II, aVF leads were observed (Fig.3). Echo observed normal myocardium contractility (EF =57%), heart with bright and a bit thick pericardium leaves with their separation up to 7 mm and 5 mm (posterior and anterior wall respectively). Chest CT revealed no abnormalities, except the amount of pericardial fluid was less than 8 mm (normally – less than 5 mm under the posterior wall of left ventricle) [2]. An acute stage of pericarditis was confirmed. Broad serological tests of infectious diseases were taken, including Brucella, Mycoplasma, CMV, VDRL, HIV, Coxsakie viruses, EBV and rheumatic factors. Immunology panel results were positive for EBV immunoglobulins (VCA IgG, EBNA IgG, EA IgG) and PCR (EBV DNA). The following treatment for the next 5 days was initiated with ertapenem 1g, prednisolone 90 mg, ibuprofen 400 mg, omeprazole 20 mg, which resulted in clinical recovery and marked improvement by the following

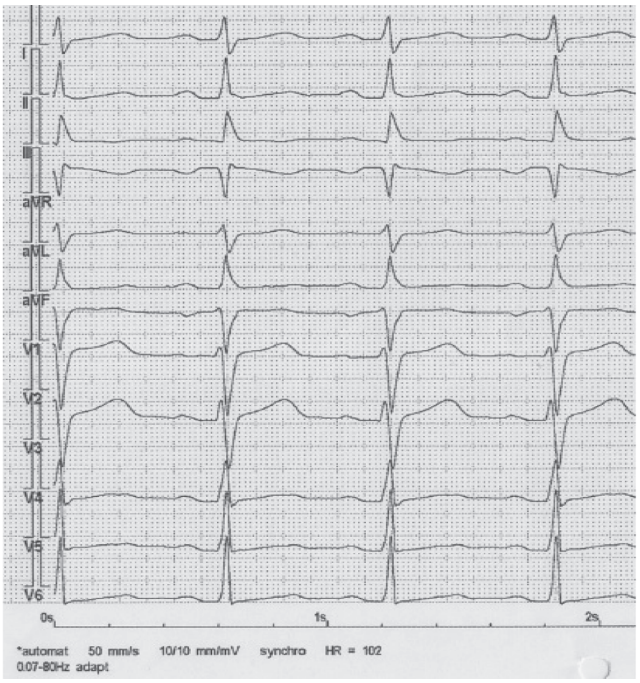

Fig. 1. ECG from a 26-year-old man with atypical chest pain for 4 days, worsened by supine position. *Stage II:* ***T-wave flattening***

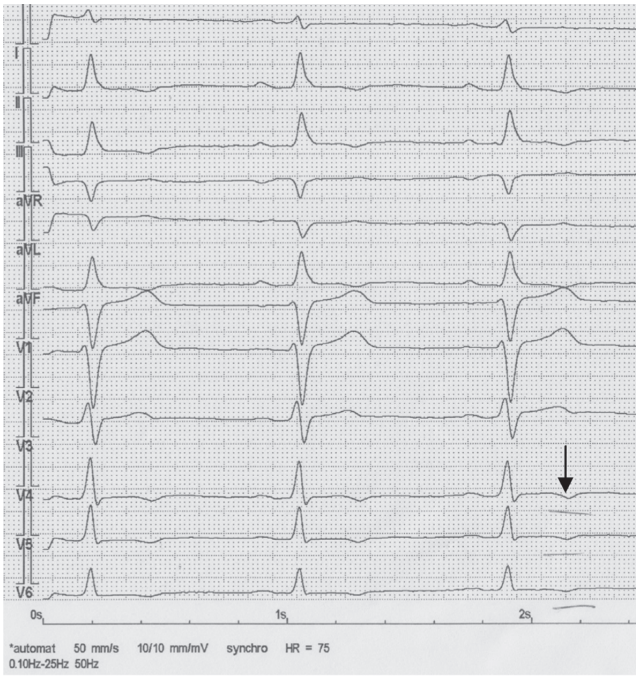

Fig. 2. ECG from the same patient one month later following treatment with NSAIDs *Stage III:* ***T-wave inversion***

days. He was discharged with a prescription for ASA and colchicine 0.5 mg once daily for three months. At one-week follow-up, the patient's symptoms had resolved and his C-reactive protein level was normal. During the follow-up after discharge the patient was doing well: no pathological changes in observation, ECG (Fig.4) and Echo examination.

Discussion

Acute pericarditis is an inflammation of the pericardium that can result in chest pain, pericardial friction rub, and serial ECG changes. [3] Acute pericarditis may have different etiologic causes and can develop due to varied conditions.

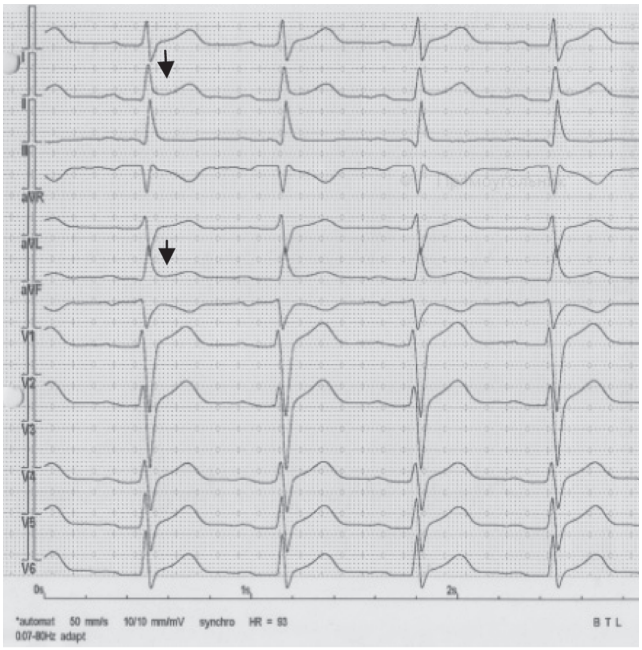

Fig. 3. ECG from 35-year old patient on the admission .
Stage I: ***Diffuse up-sloping ST-segment elevation seen in leads I, II, aVL with concordance of T waves; ST-segment depression in V1.***

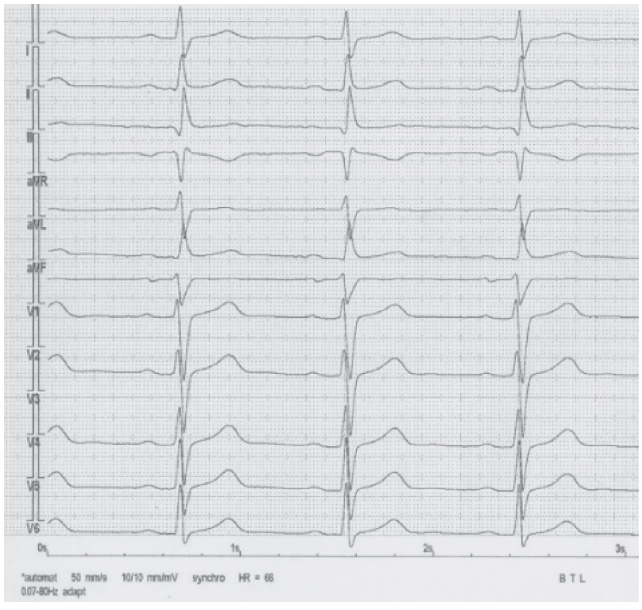

Figure 4. ECG from 35-year old patient 7 days after admission;
Stage 4: ***Gradual resolution of T-wave inversion V1***

To make an accurate diagnosis and assess for complications in patients with suspected pericarditis, updated guidelines recommend that an ECG, a transthoracic echocardiogram and a chest radiograph be obtained, as well as measurement of inflammatory markers (leukocyte count, C-reactive protein level and erythrocyte sedimentation rate) and markers of myocardial injury (cardiac troponin levels and creatinine kinase level)[4]. Other common causes of pleuritic chest pain must be ruled out, including cardiac ischemia, pneumonia, costochondritis, pulmonary embolism and substance abuse (notably cocaine).

Patients must have 2 of the following 4 clinical criteria for diagnosis: typical pericardial chest pain, pericardial friction rub, widespread ST-segment elevation or PR depression, and new or worsening pericardial effusion on echocardiography. In patients with acute pericarditis, chest pain is generally abrupt in onset; pleuritic, and substernal or left precordial in location; may radiate to the neck, arms, or jaw; and is relieved by leaning forward and worsened by lying supine. A pericardial friction rub can be detected in 85% of patients, it is best heard at the left lower border of the sternum. [4]

The 4 ECG stages of pericarditis include: 1) diffuse ST elevation and/or PR depression, 2) normalization of ST- and PR-segments, 3) diffuse T-wave inversions with isoelectric ST-segments, and 4) normalization of the ECG. Widespread ST-segment elevation has been reported as a typical hallmark sign of acute pericarditis [4,5] . However, changes in the ECG imply inflammation of the epicardium, since the parietal pericardium itself is electrically inert. Typical ECG changes have been reported in up to 60% of cases. In our cases all four stages of the ECG changes were presented. The temporal evolution of ECG changes with acute pericarditis is highly variable from one patient to another and is affected by therapy. Major differential diagnoses include acute coronary syndromes with ST-segment elevation and early repolarization.

A protocol recommendation for the patients with suspected pericarditis as the transthoracic echocardiography was provided. Echo helps in the detection, localization and quantification of pericardial effusion because the presence of an effusion helps to confirm the diagnosis, and clinical or echocardiographic evidence of tamponade indicates the need for pericardiocentesis. The appearance of the normal pericardium in M-mode or two-dimensional Echo is that of bright, dense layers of echoes inseparable from the epicardium echo (generally the pericardial echo is slightly greater than 2 mm). The size of the effusion may be graded as small (echo-free space in diastole ‹ 10 mm), moderate (10-20 mm) and large (›20 mm))[1] . In our cases pericarditis was non-effusive, that is why Echo allowed evaluating thickness of pericardium. Assessment of markers of inflammation (i.e. CRP) and myocardial injury (i.e. CK, troponin) is recommended in patients with suspected acute pericarditis. Plasma troponin concentrations are elevated in a finding that is thought to be caused by epicardial inflammation rather than myocardial necrosis. Elevation of markers of inflammation [i.e. C-reactive protein (CRP) and erythrocyte

sedimentation rate (ESR), as well as elevation of the white blood cell count] is a common and supportive finding in patients with acute pericarditis and may be helpful for monitoring the activity of the disease and efficacy of therapy[4].

Potential causes of pericarditis are numerous and include trauma, viral infection, tuberculosis, malignant disease and autoimmune conditions. Infectious pericarditis, caused by viruses, occurred in 30-50 %. Among viruses, which cause pericarditis are Coxsackie A9, B1-4, Echo 8, Mumps, Epstein-Barr Virus, CMV, Varicella, Rubella, parvovirus B19, adenovirus, herpes viruses, hepatitis viruses, HIV and enteroviruses etc [7]. Viral and idiopathic non-specific causes are the most prevalent etiologies and generally have a benign course [3]. EBV infection is common in the general population and has diverse clinical manifestations and complications. Sporadic cases describing EBV-associated acute pericarditis have been described in the medical literature emphasizing the connection between infectious mononucleosis and pericarditis [8-10]. However, in these current cases, no signs of infectious mononucleosis were observed. Diagnosis were based on the results of ECG, Echo, positive serology and PCR for EBV, and by exclusion of other viral etiologies [9]. Observational studies in developed countries have shown that the search for causative factors is often fruitless, because the condition is deemed to be idiopathic in more than 80% of patients. The diagnosis of viral pericarditis is not possible without the evaluation of pericardial effusion, preferably by PCR or in-situ hybridization. A fourfold rise in serum antibody levels is suggestive but not diagnostic for viral pericarditis. Routine viral serology is not recommended, with the possible exception of HIV and HCV patients. [11,12] Acute viral pericarditis often presents as a self-limited disease, with most patients recovering without complications.

Acute pericarditis has generally a brief and benign course after empiric treatment by non-steroidal anti-inflammatory drugs, and routine hospitalization of most patients may be unnecessary. Our patients without severe features were managed as outpatients with empiric anti-inflammatories and short-term follow-up after one week to assess the response to treatment. Treatment is primarily directed at reducing the severity and duration of symptoms and the risk of recurrence. ASA or NSAIDs are recommended as first-line therapy for acute pericarditis with gastroprotection. The therapy is based on antimicrobial and NSAIDs: in our cases ibuprofen, diclofenac were prescribed. Colchicine appeared to be effective in combination with ibuprofen in pericarditis treatment [4,13]. As the result, it was not necessary to prescribe glucocorticosteriods. Treatment is typically given for one to two weeks if a first episode and for two to four weeks if a recurrent episode, with tapering over three months.

Conclusion EBV-associated acute pericarditis may develop without any signs of the infectious mononucleosis in young and almost healthy patients. Such pathological condition may be effusive or non-effusive. Echo and ECG are the main instrumental investigations, which allow to provide the correct diagnosis. Patients usually require non-specific symptomatic treatment using NSAIDs, colchicine and glucocorticoids. It is important to be able to determine a variety of possible viruses for the confirmation of the diagnoses of acute pericarditis.

Reviewer: Corresponding Member NAMS Ukraine, professor V.Z.Netiazhenko

Conflict of interests.

Author indicate that there is no conflict of interests that would prejudice the impartiality of the research.

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ОСТРЫЙ ПЕРИКАРДИТ, АССОЦИИРОВАННЫЙ С ЕПШТЕЙН-БАРР ВИРУСОМ: ДВА СЛУЧАЯ

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Резюме. Представлены два случая неэкссудативного острого перикардита, вызванного серологически доказанным Эпштейн-Барр вирусом. У практически здоровых молодых мужчин были жалобы о внезапно возникшей резкой загрудинной боли, которая появилась во время дыхания или движения. Другие распространенные причины боли в груди должны быть исключены, в том числе ишемия сердца, пневмония, остеохондроз, легочная эмболия и токсикомания (кокаин). Прошлый анамнез был без особенностей, они отрицали недавний прием лекарств. При физикальном обследовании перикардиальный шум трения аускультативно не выслушивался, рентгенографическое исследование выявилось без особенностей. В 2015 обновленные Европейским кардиологтческим обществом принципы для диагностики и лечения заболеваний перикарда рекомендуют ЭКГ, Эхо, измерение воспалительных маркеров или повреждения миокарда. Представлены снимки и обсуждение ЭКГ типичных изменений и эхокардиографических признаков, что подтвердило диагноз острого перикардита . Возможные причины перикардита многочисленны и включают в себя травмы, вирусные инфекции, туберкулез, злокачественные заболевания и аутоиммунные условия. Поиски причинных факторов часто бесплодны, потому что зачастую они признаются идиопатическими. Общеизвестно, что вирусы могут привести к острому перикардиту, но только несколько случаев EBV-ассоциированных перикардитов уже опубликовано ранее. Определялся широкий спектр серологических тестов различных инфекционных заболеваний. Эпштейн-Барр ассоциированный выпотной или невыпотной перикардит может развиваться без каких-либо признаков инфекционного мононуклеоза у молодых и практически здоровых пациентов. Оба пациента полностью восстановились после назначения специальной нестероидной противоспалительной и колхицина терапии.

Ключевые слова: острый перикардит, вирус Эпштейна-Барр, ЭКГ-изменения, трансторакальная ЭХО.

ГОСТРИЙ ПЕРИКАРДИТ, АСОЦІЙОВАНИЙ З ЕПШТЕЙН-БАРР ВІРУСОМ: ДВА ВИПАДКИ

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Резюме. Представлені два випадки неексудативного гострого перикардиту, викликаного серологічно доведеним Епштейн-Барр вірусом. У практично здорових молодих чоловіків були скарги про раптово виниклий різкий загрудинний біль, який з'явився під час дихання або руху. Інші поширені причини болю в грудях повинні бути виключені, у тому числі ішемія серця, пневмонія, остеохондроз, легенева емболія і токсикоманія (кокаїн). Минулий анамнез був без особливостей, вони заперечували недавній прийом ліків. При фізикальному обстеженні перикардіальний шум тертя аускультативно не вислуховувався, рентгенографічне дослідження виявилося без особливостей. У 2015 оновлені Європейським кардіологтчним товариством принципи для діагностики та лікування захворювань перикарда рекомендують ЕКГ, Ехо, вимір запальних або пошкодження міокарда маркерів. Представлені приклади та обговорення ЕКГ типових змін і ехокардіографічних ознак, що підтвердило діагноз гострого перикардиту. Можливі причини перикардиту численні і включають в себе травми, вірусні інфекції, туберкульоз, злоякісні захворювання і аутоімунні умови. Пошуки причинних факторів часто безплідні, тому що найчастіше вони визнаються ідіопатичними. Загальновідомо, що віруси можуть призвести до гострого перикардиту, але тільки декілька випадків EBV-асоційованих перикардитів було опубліковано раніше. Визначався широкий спектр серологічних тестів різних інфекційних захворювань. Епштейн-Барр асоційований випотний або невипотний перикардит може розвиватися без будь-яких ознак інфекційного мононуклеозу у молодих і практично здорових пацієнтів. Обидва пацієнти повністю відновилися після призначення специальних нестероїдних протизапальних засобів і терапії колхіцином.

Ключові слова: гострий перикардит, вірус Епштейна-Барр, ЕКГ-зміни, трансторакальна ЕХО.