Clinical case

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LATE COMPLICATIONS AFTER THERAPY IN PATIENT WITH HODGKIN'S LYMPHOMA

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During the past five decades, dramatic progress has been made in the development of curative therapy for hematologic malignancies, including Hodgkin's Lymphoma (HL). The therapy responsible for this survival can also produce adverse long-term health-related outcomes, referred to as «late effects», which manifest months to years after completion of cancer treatment.

The purpose of this report is to pay attention to the problem of late complications, which develop in distant period after combined therapy of HL on example of illustrative clinical case.

KEY WORDS: Hodgkin's Lymphoma, treatment complications, pericardial effusion, heart failure, pneumofibrosis, chronic kidney disease

ПІЗНІ УСКЛАДНЕННЯ ТЕРАПІЇ У ПАЦІЄНТКИ З ЛІМФОМОЮ ХОДЖКІНА

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Протягом останніх п'ятдесяти років медицина досягла значних успіхів в лікуванні онкогематологічних захворювань. Терапія, завдяки якій були досягнуті ці результати, згодом може призводити до ускладнень, званими «пізніми ефектами». Останні можуть маніфестувати від декількох місяців до декількох років після завершення лікування лімфоми.

Мета цієї статті - на наочному прикладі клінічного випадку звернути увагу на проблему пізніх ускладнень, які розвиваються в віддаленому періоді після комбінованої терапії лімфоми Ходжкіна.

КЛЮЧОВІ СЛОВА: лімфома Ходжкіна, ускладнення терапії, перикардіальний випіт, серцева недостатність, пневмофіброз, хронічна хвороба нирок

ПОЗДНИЕ ОСЛОЖНЕНИЯ ТЕРАПИИ У ПАЦИЕНТКИ С ЛИМФОМОЙ ХОДЖКИНА

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В течение последних пятидесяти лет медицина добилась значительных успехов в лечении онкогематологических заболеваний. Терапия, благодаря которой были достигнуты эти результаты, впоследствии может приводить к осложнениям, называемым «поздними эффектами». Последние могут манифестировать от нескольких месяцев до нескольких лет после завершения лечения лимфомы.

Цель настоящей статьи – на примере показательного клинического случая обратить внимание на проблему поздних осложнений, которые развиваются в отдаленном периоде после комбинированной терапии лимфомы Ходжкина.

КЛЮЧЕВЫЕ СЛОВА: лимфома Ходжкина, осложнения терапии, перикардиальный выпот, сердечная недостаточность, пневмофиброз, хроническая болезнь почек

INTRODUCTION

With advances in therapy, HL has become highly curable, with survival rates approaching 95 % for patients with early-stage disease and 75 % for those with advanced disease [1–3]. Unfortunately, the improved prognosis of HL has been accompanied by elevated risks of second malignancies (leukemia, lung, stomach, breast, bone, colorectal cancers, etc.), cardiac disease (coronary artery disease, conduction abnormalities, valvular disease, pericardial disease), pulmonary dysfunction, infections, endocrinopathy.

Researches have demonstrated that late effects contribute to a high burden of morbidity, including the following: 60 % to more than 90 % develop one or more chronic health conditions; 20 % to 80 % experience severe or life-threatening complications. Investigations demonstrated that the elevated risk of morbidity and mortality among aging survivors in the cohort increases beyond the fourth decade of life. By age 50 years, the cumulative incidence of a self-reported severe, disabling, life-threatening, or fatal health condition was 53.6 % among survivors, compared with 19.8 % among a sibling control group. Among survivors who reached age 35 years without a previous severe, disabling, life-threatening health condition, 25.9 % experienced a new severe to fatal health condition within 10 years, compared with 6.0 % of healthy siblings [4]. The presence of serious, disabling, and life-threatening chronic health conditions adversely affects the health status of aging survivors, with the greatest impact on functional impairment and activity limitations. Female survivors demonstrate a steeper trajectory of age-dependent decline in health status compared with male survivors [5]. The even higher prevalence of late complications among clinically ascertained cohorts is related to the subclinical and undiagnosed conditions detected by screening and surveillance measures [6].

CLINICAL CASE

Our patient was 37 year old well-groomed and good mood female. On admission patient suffered from dyspnea during exertion (especially when going uphill or upstairs), even ordinary physical activity provoked breathlessness, ankles edema in the evening, face and eyelid puffiness in the morning, palpitations, tendency to hypotension (85/55 mm Hg).

In 1993, when she was 15 years old, Hodgkin's Lymphoma of mandibular, cervical, intrathoracic lymph nodes had been diagnosed. The combination therapy had been carried out, but particular regimens and medicines patient currently do not remember. Bilateral cervical, supra-, infraclavicular, axillar as well as mediastinal regions radiotherapy had been performed. Since 1996 remission occurs, relapses did not observe.

During last three years dyspnea and ankle swelling bother the patient. She was surveyed in cardiologic center and for the first time was established diagnosis «Mild pericardial effusion. Chronic congestive heart failure II FC NYHA». It was prescribed: salt restriction in diet (< 3 g per day), torasemide 5 mg in the morning and ivabradine 7.5 mg. Symptoms decreased (but not completely ceased), exercise tolerance slightly improved. During the last month dyspnea and exercise intolerance were exacerbated, even ordinary physical activity and walking ground level less then 500 m led to breathlessness. Also palpitations had developed. Due to symptoms deterioration, patient had been referred to cardiologic department.

Examination revealed following changes. The general condition of the patient was satisfactory, she was not in distress. Not obese. On the lower part of the neck to the left presented small scar due to lymph node biopsy in 1995. Mild ankle edema was detected. All groups of lymph nodes were not palpable, in the axillary region to the right palpated dense scar tissue (painless, possibly post beam therapy). No visible enlargement of thyroid gland, but it was palpated, size was slightly increased, painless, had smooth surface, homogeneous structure, nodules were not detected. JVP 4.7 cm was above the sternal angle. Lungs to auscultation vesicular breath sounds. Apex beat localized in the 5^{th} intercostal space, diffuse and diminished force. Heart to auscultation: S1 and S2 were soft, systolic murmur heard over mitral valve, pericardial friction rub along the left sternal border. Abdomen was soft and nontender. Liver: percussion – 13/12/9 cm, palpated 4 cm lower than right costal arch, nontender and soft, and had smooth surface. Spleen: percussion – 10/15 cm, palpated 6 cm lower than left costal arch, tenderless, had elastic consistency and smooth surface. The

kidneys were not palpable. Stool and diuresis were unremarkable.

Clinical data revealed following findings. Complete blood count and urine analysis were unremarkable. Plasma glucose, liver function tests, ESR, C-RP, ASL-O, RF, thyroid hormones fell in reference range. Kidney function was decreased: serum creatinine 97 mkmol/L, eGFR = 60 ml/min/1.73m^2 (by MDRD formula). Also it was occurred diuretic induced iatrogenic hypokalemia (3.2 mmol/L). ECG revealed sinus tachycardia (110 bpm), electrical alternant, complete RBBB, left ventricle overload, PR-segment depression in II, III, AVF, PR-segment elevation in AVR, ST-segment depression in I, II, III, AVF, V1-V6, ST-segment elevation in AVR, V1. On Holter ECG monitoring was not detect rhythm abnormalities. Echocardiography found mild pericardial effusion (echo-free pericardial space up to 7 mm), aortic fibrosis myocardial contractility was preserved EF 75 %, but heart chambers were diminished in size and cardiac output was only 47 ml. Chest CT scan detected lung roots fibrosis and cardiomegaly with mild hydropericardium (maximal fluid thickness 14 mm), minimal upper mediastinal lymphadenopathy with no reliable progression by comparison with 2008 year. Abdomen ultrasound detected hepatosplenomegaly (liver: right lobe 15,5 cm, left lobe 8 cm; spleen: 7.5 cm/15 cm), diminished left kidney about two times of normal (hypoplasia? or drug nephrotoxicity?), urolithiasis.

Based on complaints, patient's past medical history, and physical examination final diagnosis had been established:

Main disease. Hodgkin's Lymphoma, remission

Complications. Late Hodgkin's lymphoma therapy complications: chronic mild pericardial effusion, diffuse cardiosclerosis following aseptic myocarditis, aortic valve sclerosis, sinus tachycardia, right bundle branch block, chronic congestive heart failure with preserved EF (75 %), II FC NYHA, hypoplasia? (drug induced atrophy?) of the left kidney, CKD II stage, hepatomegaly with splenomegaly, diffuse nodular non-toxic goiter.

Management of the patient is directed to the improvement of patient's symptoms and quality of life. It was recommended follow the diet low sodium and rich in potassium. For rate control it was prescribed ivabradine 7.5 mg bid. To prevent edema toracemide 5 mg was recommended. For hypokalemia correction potassium chloride 600 mg bid under control of serum potassium was prescribed. To prevent heart failure progression low doses of ACE-inhibitor ramipril 1.25 mg was recommended. For pericardial effusion was recommended low doses of NSAIDs, aspirin 500 mg under gastroprotection by PPI inhibitors pantoprazole 40 mg.

Outcome. Despite of therapy, pericardial effusion persist by control echocardiography data, amount of pericardial fluid was not change. Symptoms ceased, physical tolerance slightly increased, but lower extremities edema and morning eyelid puffiness was observed.

CONCLUSIONS

Patients, who have been treated for Hodgkin's disease, despite being cured of their malignancy, may develop iatrogenic complications that lead to premature mortality. A substantial excess risk of mortality may be attributable to second cancers and cardiac diseases. Multitude of patients has been treated with anthracyclines or chest radiation, both of which may cause cardiovascular and kidney damage. The frequency of long-term complications in patients treated for Hodgkin's disease makes continued follow-up an important part of their care. This follow-up should include efforts to prevent morbidity and mortality by early diagnosis and attention to risk factors. Future treatment regimens for Hodgkin's disease should be designed attempting to minimize these complications.

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