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ХРОНИЧЕСКАЯ СЕРДЕЧНАЯ НЕДОСТАТОЧНОСТЬ С СОХРАНЕННОЙ ФРАКЦИЕЙ ВЫБРОСА У КОМОРБИДНОГО ПАЦИЕНТА: ВОПРОСЫ ВЕРИФИКАЦИИ «СЛОЖНОГО» ДИАГНОЗА

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Chronic Heart Failure with Preserved Ejection Fraction in A Comorbid Patient: Issues in Verification of A «Difficult» Diagnosis

Резюме

Хроническая сердечная недостаточность с сохраненной фракцией выброса (ХСНсФВ) — это сложный, гетерогенный, полиорганный системный синдром, который характеризуется значительной заболеваемостью и смертностью. В настоящее время он приобрел характер эпидемии XXI века. В клиническом наблюдении описана история пациентки пожилого возраста, страдающей ишемической болезнью сердца (ИБС), дислипидемией, стенозирующим атеросклерозом брахиоцефальных артерий на фоне артериальной гипертензии (АГ), ожирения, сахарного диабета (СД) 2 типа, осложненного диабетической ретинопатией, полинейропатией, нефропатией с развитием хронической болезни почек (ХБП) и ХСНсФВ. Состояние отягощалось наличием хронического пиелонефрита единственной почки после нефрэктомии справа по поводу абсцесса почки, бронхиальной астмы. Продемонстрированы ограничения в использовании современных шкал для определения предтестовой вероятности ХСНсФВ, низкий показатель натрийуретических пептидов (НУП). Коморбидность, плохо контролируемые АГ, СД, низкая приверженность к терапии привели к развитию острой сосудистой катастрофы, повторное нарушение мозгового кровообращения — к летальному исходу. Гистологически обнаружен выраженный периваскулярный и интерстициальный склероз в миокарде и эпикарде, который является основой диастолической дисфункции при ХСНсФВ.

Клинический пример отражает трудности диагностики ХСНсФВ, а также взаимное патогенетическое влияние сопутствующей патологии, что привело к неблагоприятному исходу при несоблюдении рекомендаций.

Ключевые слова: *хроническая сердечная недостаточность, сохраненная фракция выброса, фиброз миокарда, коморбидность*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Chronic heart failure with preserved ejection fraction (HFpEF) is a complex, heterogeneous, multi-organ systemic syndrome characterized by significant morbidity and mortality. Currently, it has acquired the character of an epidemic of the 21st century.

The clinical observation describes a typical story of an elderly patient suffering from coronary artery disease (CAD), dyslipidemia, atherosclerosis of the brachiocephalic arteries against the background of arterial hypertension (AH), obesity, type 2 diabetes mellitus (DM), complicated by diabetic retinopathy, polyneuropathy, nephropathy with development of chronic kidney disease (CKD) and HFpEF. The condition was aggravated by the presence of chronic pyelonephritis of a single kidney (right nephrectomy for renal abscess in 2013), bronchial asthma. The limitations of modern scales for determining the pre-test probability of HFpEF and low natriuretic peptide levels are demonstrated. Comorbidity, poorly controlled hypertension, diabetes, low adherence to therapy led to the development of acute vascular accident, then, repeated cerebrovascular accident — to a fatal outcome. Histologically, perivascular and interstitial sclerosis in the myocardium and epicardium was detected, which is the basis of diastolic dysfunction in HFpEF.

A clinical example reflects the difficulties of verification of HFpEF-diagnosis, as well as the mutual pathogenetic influence of concomitant pathology, which can lead to an unfavorable outcome if recommendations are not followed.

Key words: *chronic heart failure, preserved ejection fraction, myocardial fibrosis, comorbidity*

Conflict of interests

The authors declare no conflict of interests

Conformity with the principles of ethics

Informed consent is not required due to the impossibility of identifying the patient

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AH — arterial hypertension, BP — blood pressure, IHD — ischaemic heart disease, BMI — body mass index, LV — left ventricle, NUP — natriuretic peptides, DM — diabetes mellitus, LVEF — left ventricular ejection fraction, FC — functional class, CKD — chronic kidney disease, CCFwEF — chronic heart failure with preserved ejection fraction, echoCG — echocardiography

Introduction

A comorbidity (especially DM, AH, obesity and atrial fibrillation) is an underlying factor for CCFwEF. Nowadays, the number of patients with excessive body weight, impaired lipid and carbohydrate metabolism, renal dysfunction is constantly growing; these conditions trigger cellular and molecular changes in cardiac tissues: inflammation; fibrosis; impaired nitrogen oxide synthesis; sarcomere dysfunction; mitochondrial and metabolic diseases, which result in diastolic dysfunction, a key component in the development of CCFwEF [1]. Clinical phenotyping of CCFwEF is essential for selection of an individualised approach to the therapy. Patients with cardiac-renal-metabolic phenotype who have obesity, IHD, DM2, CKD, have poor prognosis and are at a high risk of all-cause death of hospital admission due to CCF [2]. Higher acute cardiovascular mortality rates in patients with abdominal obesity, dyslipidaemia, AH and hyperglycaemia are associated with endothelial dysfunction caused by insulin resistance, which is a universal vascular wall defect [3]. CCFwEF diagnosis in the real clinical practice is often challenging. Current clinical recommendations regulate diagnosis based on specific complaints, confimred with objective signs (or reaction to diuretics), markers of left ventricle diastolic dysfunction seen on echoCG, as well as higher natriuretic peptide levels. It is recommended to use H2FPEF and HFA-PEFF scales; and if there are minor dystolic dysfunction and other contradictory examination results, diastolic stress test should be used, which is not readily available in our country [4].

We are discussing a case study here, which reflects the characteristics and challenges with CCFwEF diagnosis in a cardiac-renal-metabolic patient.

Case Study

Here is the medical record of Patient S. (Figure 1), who was followed up in the outpatient clinic of City Clinical Hospital No. 11. In November 2023, the patient started complaining of shortness of breath and retrosternal pain after physical exercises, elevated blood pressure (BP) of up to 160/100 mm Hg, headache, general weakness, occasional ankle swelling.

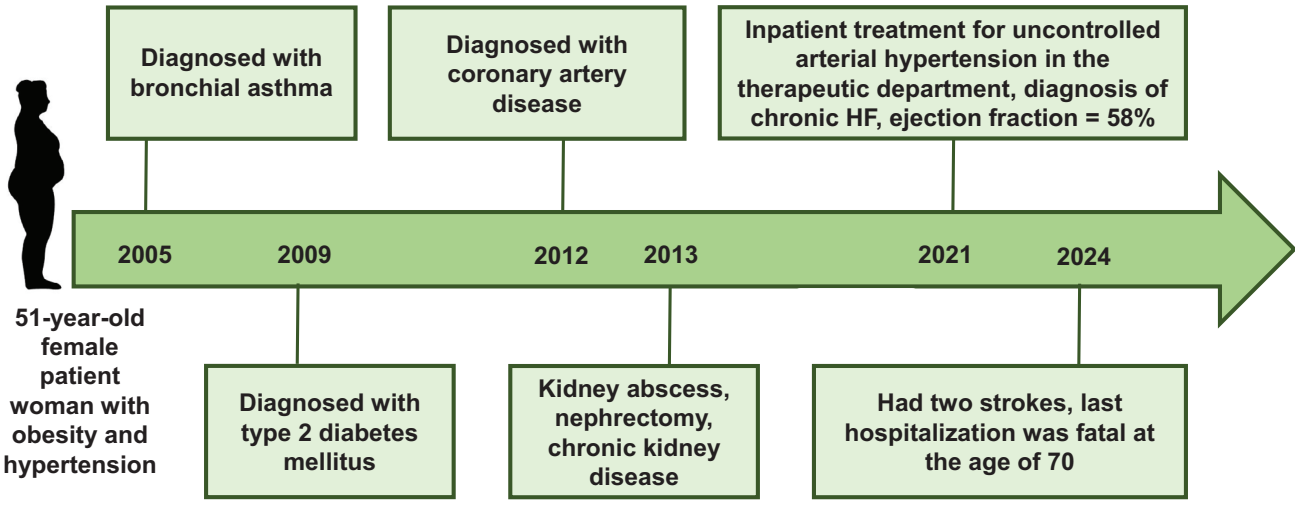

Figure 1. *Timeline of development of the cardiorenometabolic continuum and its outcomes in the observed patient*

According to her medical record, the patient had been suffering from hypertension since 1997; she did not take any regular antihypertensive drugs, usually when her BP was elevated. Then she was diagnosed with broncial asthma, which was treated with budesonide + formoterol (partial control of symptoms was achieved). Later she was diagnosed with DM2, her medications included various combinations of metformin, glibenclamide, gliclazide, vildagliptin. The patient was diagnosed with IHD, exertional angina, functional class (FC) II; she was taking acetylsalicylic acid, statins, nitroglycerine when needed, courses of trimetazidine, nicorandil. CKD developed as a result of BP, DM and prior right nephrectomy because of an abscess. In 2021, she was treated in an inpatient internal medicine ward of City Clinical Hospital No. 11, where CCFwEF was diagnosed for the first time (left ventricle ejection fraction (LVEF) = 58 %). The patient was not hospitalised any more, her condition worsened from November 2023. Life history: disabled person of group 2 from 2011; during the follow-up, she worked as a receptionist in a musical school (work in day-long shifts). Objective findings: height — 150 cm, weight — 85 kg, body mass index (BMI) — 37.7 kg/m^2. Waist circumference: 114 cm. Oxygen saturation is 98 %. The condition is satisfactory, and consciousness is clear. Vesicular breathing with individual dry rales in lower sections with forced expiration. Respiratory rate is 18/minute. Auscultation of the heart: muffled heart tones, regular rhythm; heart rate is 64 bpm; BP: 150/90 mm Hg. The abdomen is soft and non-tender on palpation. Ankle and feet pastosity. Bowel and bladder functions are within normal. Laboratory and instrumental test results: N-terminal pro B type natriuretic peptide (NT-proBNP) (31/10/2023) — 106.8 pg/mL; complete blood count (28/11/2023): elevated erythrocyte sedimentation rate (25 mm/h), otherwise unremarkable; urinalysis (27/11/2023): protein traces, albuminuria test strip testing: 20 mg/L. Blood biochemistry (27/11/2023): total cholesterol 7.2 mmol/L, high density lipoproteids 1.3 mmol/L, low density lipoproteids 4.9 mmol/L, plasma glucose 8.1 mmol/L, glicated haemoglobin 7.9 %, creatinine 112 μmol/L, glomerular filtration rate 43.2 mL/min/1.73m^2. Electrocardiography (27/11/2023): axis deviation to the left, sinus rhythm with heart rate of 70–77 bpm, signs of left ventricular (LV) hypertrophy, diffuse changes in the miocardium. Annual chest X-ray fluorography: no pathological shadows. Diagnosis: IHD, exertional angina, FC 2. Atherosclerosis of aorta and brachiocephalic arteries. Stage 3 hypertension, uncontrolled. LV hypertrophy. Degree 2 obesity. Dyslipidemia. Type 2 diabetes mellitus, diabetic retinopathy, polyneuropathy, nephropathy. Stage 3B CKD, stage A1 albuminuria. Risk grade 4 (very high). Stage 2A CCFwEF, FC 2 (LVEF 64 %). Chronic pyelonephritis of the remaining kidney (right nephrectomy because of an abscess, 2013). Mild persistent bronchial asthma (mixed genesis), controlled. Chronic cholecystitis, remission. Dorsopathy resulting from lumbar osteochondrosis, remission. The patient was consulted by a cardiologist, endocrinologist, lung specialist; commendations: losartan 100 mg/day; bisoprolol 2.5 mg/day; nitroglycerine 0.5 mg as required; torasemide 2.5 mg/day; atorvastatin 40 mg/day; acetylsalicylic acid 100 mg/day; metformin 2,000 mg/day; gliclazide 60 mg/day; vildagliptin 100 mg/day; budesonide + formoterol 400 + 12 μg/dose, 2 inhalations daily; ipratropium bromide + fenoterol 20 + 50 μg/dose, 2 inhalations as required. Patient's Morisky-Green (MMAS-8) compliance score is four points, i.e. poor compliance. After torasemide therapy, the patient noted improvement in swelling, shortness of breath after physical exercises, and discontinued the drug by herself one month later. She explained the inconsistencies in taking the medications and insufficient dosages by a large number of prescribed products, complicated dosage regimens, high cost of therapy, and irregularities in supply of subsidized

drugs. In March 2024, the patient underwent brachiocephalic artery duplex ultrasound scanning (11/03/2024): signs of atherosclerosis of brachiocephalic arteries, stenotic left internal carotid artery (up to 65 %) in its proximal section. Left vertebral artery hypoplasy. EchoCG (11/03/2024): LV end-diastolic diameter — 4.9 cm; LV end-sistolic diameter — 3.2 cm; LV end-diastolic volume — 110 mL; LV end-sistolic volume — 39 mL; LVEF — 64 %; interventricular septum thickness — 1.4 cm; diastolic LV posterior wass thickness — 0.9 cm; LV myocardial mass index — 116 g/m^2, relative LV wall thickness — 0.56; left atrium — 43*54*38 mm; indexed left atrium volume — 27.7 mL/m^2, pulmonary artery systolic pressure — 20 mm Hg; E/e' — 14. 6-minute walking test: 389 m, corresponding to FC 2. H2FPEF score: 5 points; HFA-PEFF score: 2 points. Intermediate probability of CCFwEF [4]. On 17/04/2024, the patient visited the emergency room at the outpatient clinic complaining of high blood pressure (160/100 mm Hg), headache, dizziness, shortness of breath during walking. Her antihypertensive therapy was corrected: amlodipine 2.5 mg/day and moxonidine 0.2 mg/day were added, a sick note was initiated because of uncontrolled AH. When on 22/04/2024 her blood pressure rose to 190/100 mm Hg, the patient started experiencing unsteady gait, blackouts, weakness in her lower extremities; she did not call for ambulance, as her next GP and endocrinologist appointments were due on 23/04/2024. Consultation by GP dated 23/04/2024: BP 160/100 mm Hg, talks with difficulties, marked weakness in her limbs, unsteady gait. Electrocardiography findings: no signs of acute coronary pathology. The neurologist urgently referred the patient to the neural vascular ward at City Clinical Hospital No. 11 with suspected acute cerebrovascular event, where the patient was treated from 23/04/2024 to 13/05/2024 for ischemic stroke in the vertebrobasilar system with dysarthria, atherothrombotic subtype, with secondary brainstem syndrome. EchCG (23/04/2024): LVEF — 60 %, E/e' — 14, left atrium volume index — 24 mL/m^2, left ventricle myocardium mass index — 110 g/мм^2, pulmonary artery systolic pressure — 20 mm Hg. The patient was discharged for the follow-up by neurologist and GP; recommendations: lisinopril 20 mg/day, amlodipine 5 mg/day, atorvastatin 40 mg/day, ezetemibe 10 mg/day, acetylsalicylic acid 100 mg/day, gliclazide 90 mg/day, sitagliptin 100 mg/day. Home visit (14/05/2024): stays is bed, double incontinence, quadriparesis, dysarthria, requires assistance. Since on 18/05/2024 the patient's condition and speech function deteriorated, her shortness of breath at rest worsened, the patient was admitted to the neural vascular ward at City Clinical Hospital No. 11 and connected to an invasive mechanical ventilation apparatus, where she died on 19/05/2024. A postmortem examination revealed ischaemic brainstem stroke; myocardial hypertrophy (heart weight: 398 g, left ventricle wall thickness: 1.6 cm, interventricular

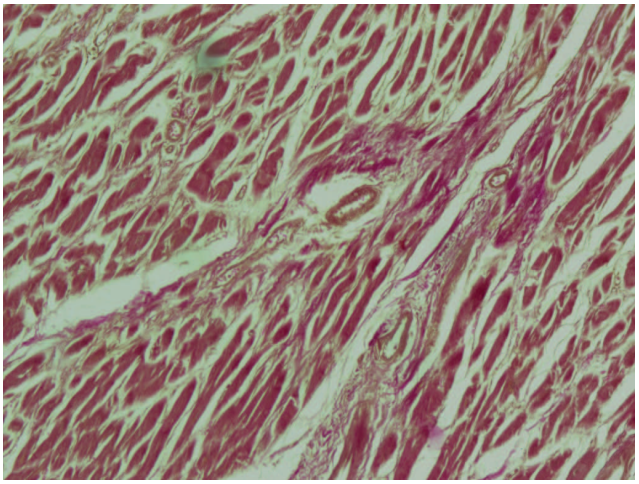

Figure 2. *Fragment of the myocardium.*
Note. Van Gieson's staining. The connective tissue in the perivascular and interstitial zone turned bright pink. Edema of the interstitium and hypertrophy of cardiomyocytes

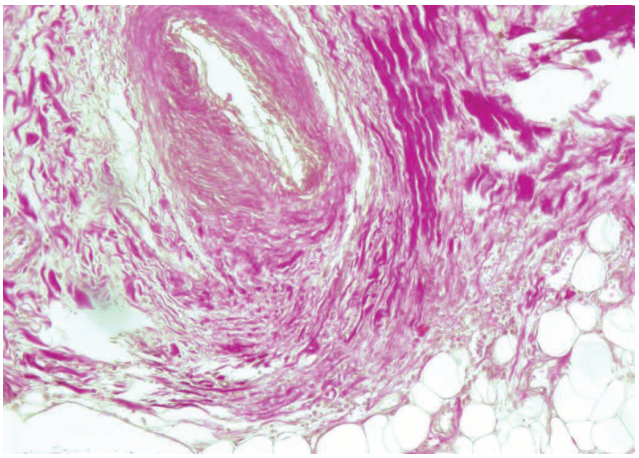

Figure 3. *Fragment of the epicardium*
Note. Van Gieson's staining. The connective tissue in the perivascular zone turned bright pink (severe sclerosis of the vessel walls)

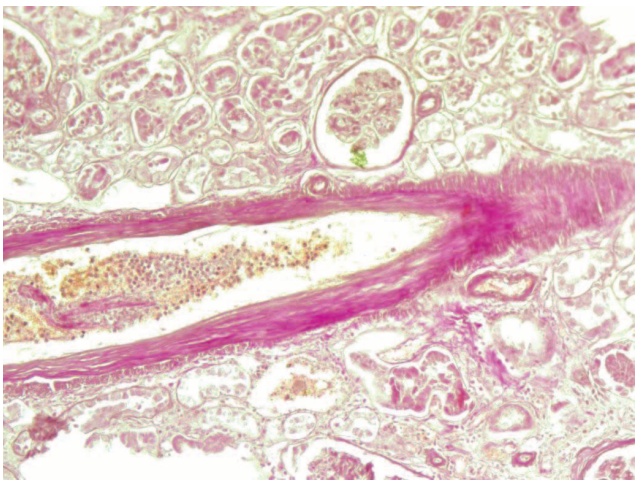

Figure 4. *A kidney fragment*
Note. Van Gieson's staining. The connective tissue in the perivascular zone and the connective tissue in the stroma of the organ. Necrobiosis of the tubular epithelium

septum: 1.6 cm); enlarged cardiac cavities; macrofocal cardiosclerosis of the lower wall of the left ventricle (old grey 2.2 cm scar); obliterating atherosclerosis of coronary arteries (grade 3, stage 3, stenosis 56 %); chronic general congestion of internal organs: nutmeg liver, congestive splenomegaly, swelling of subcutaneous tissue of lower limbs; chronic pyelonephritis attack. Heart tissue histology showed marked interstitial and perivascular fibrosis (Figure 2, Figure 3).

Discussion

Patients with CCFwEF have comorbidities; every second patient has over five non-cardiac comorbidities; the process is triggered by a combination of risk factors and associated conditions, including age, female sex, hypodynamia, obesity, atrial fibrillation, IHD, DM, dyslipidemia, AH, metabolic syndrome, CKD, anaemia, chronic obstructive pulmonary disease, and sleep apnea. There are no specific diseases, which could be a clear cause of CCFwEF, since this condition is inflammatory or metabolic [5]. There are no specific symptoms or signs of CCFwEF; they are similar to those in patients with cardiac failure: shortness of breath, poor tolerance of physical activities, fatigue, chest discomfort [6]. The patient had signs and symptoms of CCF, diastolic dysfunction seen on echo CG, which, even in the absence of elevated NT-proBNP confirms CCFwEF, despite insufficient HFA–PEFF and H2FPEF score [4]. In the real-time clinical practice, diagnostic algorithms are often not used due to NUP testing unavailability, poor availability of modern ultrasound units at outpatient clinics, and impossibility for the functional diagnostics specialists to examine the diastole in detail. Thorough echoCG examination is fundamental for the diagnosis of diastolic dysfunction and CCFwEF verification. Myocardial fibrosis caused by inflammatory and metabolic disorders makes cardiac cavities more rigid, resulting in higher LV filling pressure and left atrium pressure. A non-invasive marker of this process is E/e' — a ratio between the force, the left atrium has to overcome to fill LV with blood during diastole, and the rate of LV relaxation. However, during echoCG only 20.6 % of functional diagnosis specialists measure Simpson's LVEF; 13.5 % still use the Teicholz method; 62.6 % use both methods, and 3.2 % don't measure LVEF at all. Indexed left atrium volume is routinely measured by 56.8 % of medical professionals, E/e' is measured by 51.6 %; echoCG speckle-tracking and diastolic stress test are rare. Under these circumstances, symptomatic comorbid patients with obesity, DM, atrial fibrillation, CKD are in the grey area for the assessment of the probability of CCFwEF using modern scales [7, 8]. Clinical measurements of NUP values shifted the paradigm in the management of CCF patients; however, NT-proBNP is not an ideal biomarker of CCFwEF. The value ruling out this condition is below 125 pg/mL; and patient previously treated for CCF can have lower values [4]. There are causes of elevated NUP levels: elderly age, CKD, acute coronary syndrome, pulmonary hypertension, pulmonary embolism, transient elevation during initiation of valsartan + sacubitril, use of cardiotoxic medicines, atrial fibrillation and other arrhythmias, sepsis, thyrotoxicosis, valvular diseases. Literature references actively discuss the NUP deficit syndrome; there are numerous factors affecting their reduction in CCF patients: obesity, pulmonary oedema, chronic cardiac compression, cardiac tamponade, gene *NPPB* polymorphism, elevated androgen levels in female patients, hypercorticoidism, insulin resistance, continuous valsartan + sacubitril therapy, elevated androgen levels, minor problems with myocardium structure and function [9, 10]. The exact feedback mechanism between obesity and NT-proBNP levels is still unknown. It is assumed that obesity increases NUP clearance in adipocytes, which can be programmed on genetical level and reduces their release. It is thought that lower NUP levels are recorded in patients with CCFwEF and obesity because of increased mechanical load for the pericardium (similar to chronic cardiac compression) [6, 11, 12]. Therefore, the current recommendation is to reduce baseline NT-proBNP values by 25 % for BMI of 30 to 35 kg/m^2; by 30 % for BMI of 35 to 40 kg/m^2, and by 40 % for BMI over 40 kg/m^2 [13]. According to this recommendation, in stage 2 obesity, the lower NT-proBNP level for the patient was 87.5 pg/mL. Also, she had factors increasing NT-proBNP levels: elderly age and CKD. Cardiac-renal-metabolic CCFwEF is widely presented in numerous studies; these are patient with obesity, DM, CKD; they can account for 1/3 of the CCFwEF population [2]. Developing metabolic disorders and inflammatory process play an important role in CCFwEF pathogenesis, and the relationship between these two biological processes is termed appropriately — metaflammation, or inflammatory-fibrous paradigm [14, 15]. Obesity, which is associated with constant low-intensity systemic inflammation, triggers a cascade of cardiac-renal-metabolic syndrome, promotes myocardium infiltration with monocytes, which release inflammatory cytokines activating fibroblasts and later causing myocardial fibrosis, underlying CCFwEF development [16, 17]. By triggering insulin resistance, obesity promotes DM development, which is diagnosed in every third patient with CCF, irrespective of impaired glucose tolerance, fasting glycemia and pre-diabetes. Even more marked microvascular inflammation in DM patients results in diffuse atherosclerosis-independent myocardial fibrosis. In uncontrolled glycemia, endothelial dysfunction worsens, vascular wall is affected by atherosclerosis, which can later result in acute circulation failure [18]. DM leads to significant reduction in NT-proBNP levels, which is a result of its higher glycosilation, which is promoted by higher blood glucose levels and insulin resistance in obese individuals [11]. DM, obesity and AH underlie CKD.

Table 1. *Management considerations for patients with a cardiorenal-metabolic profile and comorbid conditions*

Issue	Approach
Weight management and glycemic control	Low-calorie diet, increased physical activity (aerobic exercises), and consideration of GLP-1 receptor agonists. If eGFR >30 ml/min/1.73m^2, SGLT2i and metformin are the primary options [4].
Achieving target blood pressure	Avoid short-acting antihypertensive drugs. In patients with asthma, CCB and ARB are preferable, as they are less likely than ACEi to induce cough [20, 21].
Preserving kidney function	Initiate treatment with low doses and titrate up carefully while monitoring eGFR and electrolytes. Avoid any medications without prior consultation with a physician [4, 20].
Lipid disorders and atherosclerosis	Statins should be used to achieve LDL targets (<1.4 mmol/L or a 50 % reduction from baseline). If statins are insufficient, ezetimibe should be added [4, 21].
Bronchial asthma management	Regular use of maintenance therapy is essential. Avoid short-acting β-agonists due to their adverse cardiovascular effects, systemic glucocorticoids (which negatively impact glucose and lipid metabolism), and β-blockers unless absolutely necessary, using only at low doses [20, 21].
Patient education and preventive care	Participation in diabetes education programs and heart failure management clinics. Referral for stage 3 medical rehabilitation and routine medical follow-ups. Vaccination against influenza and pneumococcal infections [4].

Abbreviations: GLP-1 — Glucagon-like peptide-1 receptor agonists, eGFR — estimated Glomerular Filtration Rate, SGLT2i — Sodium-glucose co-transporter 2 inhibitors, CCB — Calcium channel blockers, ARB — Angiotensin receptor blockers, ACEi — Angiotensin-converting enzyme inhibitors, LDL — Low-density lipoproteins

General pathological mechanisms, general risk factors or systemic impairments affect the heart and kidneys, causing their simultaneous dysfunction. Every second CCF patient has CKD. Organ hypoperfusion resulting from inadequate heart functioning activates the renin-angiotensin-aldosterone and sympathic nervous system, oxidative stress, necrobiotic and fibrotic changes in the kidney, resulting in the development and active progression of CKD. The patient had chronic type 2 cardiorenal syndrome: impaired cardiac function caused by AH, IHD, DM, CCF, leading to progressive kidney injury; nephrectomy because of an abscess was an important factor for CKD development, which affected the renal function [19, 20].

When observing this interconnected pathological cascade, it becomes clear that monitoring blood glucose levels, BP and lipid levels in a comorbid patient is very important, and the patients should be aware not only of their diseases, but also understand that the prescribed therapy improves prognosis and prolongs their life. A disease-modifying therapy in CCFwEF patients should include sodium glucose linked co-transporter-2, renin-angiotensin-aldosterone system inhibitors, mineralocorticoid receptor antagonists [4]. Since BP was not controlled adequately, losartan replacement with candesartan, or valsartan + sacubitril should have been discussed, aldosterone antagonists should have been added [4, 21]. Failure to reach target levels of low-density lipoprotein in the patient from the very high risk group with obliterating atherosclerosis of brachiocephalic arteries requires addition of ezetemibe to the statin. Since the patient had bronchial asthma, her heart rate should have been controlled with ivabradine or dihydropyridine calcium antagonists (amlodipine/ felodipine) instead of beta blockers [4]. A combination of the mentioned medications would have provided optimal heart and kidney protection.

Conclusion

This case study demonstrates challenges with CCFwEF verification in a comorbid patient with cardiac-renal-metabolic phenotype in outpatient settings due to low NUP levels and lack of ultrasound criteria for reliable diagnosis, which restricts the use of scales and algorithms for CCFwEF verification in real-time clinical practice. Timely diagnosis and drug correction of a comorbidity, prescription of disease-modifying therapy and better compliance are the factors, which can improve prognosis.

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Пономарева О.В.: разработка концепции, написание текста рукописи, сбор данных и обработка материала, взаимодействие с редакцией в процессе подготовки публикации и печати

Смирнова Е.А.: научное руководство, разработка концепции, критический пересмотр статьи на предмет важного интеллектуального содержания, доработка текста статьи, итоговые выводы.

Шукис К.А.: проведение аутопсии, подготовка и описание гистологических микропрепаратов, предоставление иллюстративного материала, итоговые выводы.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Ponomareva O.V.: concept development, manuscript writing, data collection and material processing, interaction with the editors during the preparation of the publication and printing.

Smirnova E.A.: scientific supervision, concept development, critical revision of the article for important intellectual content, revision of the article text, final conclusions.

Shukis K.A.: autopsy, preparation and description of histological micropreparations, provision of illustrative material, final conclusions.

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