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CASE SERIES

Misdiagnosis of Chronic Heart Failure in Patients with Type 2 Diabetes Mellitus in Primary Care: A Report of Two Cases and Literature Review

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Abstract: The coexistence of heart failure (HF) and type 2 diabetes mellitus (T2DM) is common and poses a serious threat to human health because these diseases have a high degree of commonality at the vascular level. However, the diagnosis of HF in primary care can be challenging, leading to the risk of inadequate management of both conditions. Using two case reports as examples, we attempt to shed light on the issues involved in this challenge. In the first case presentation, a 62-year-old male patient with T2DM and dyspnea was initially diagnosed with HF during primary care. However, further workup revealed that the actual cause of the patient's breathlessness was the exacerbation of chronic obstructive pulmonary disease. In the second case, a 59-year-old woman with T2DM and obesity complained of leg swelling that was attributed to chronic venous insufficiency by a primary care physician. A correct diagnosis of HF with preserved ejection fraction (HFpEF) was made using N-terminal pro-B-type natriuretic peptide and echocardiography. Due to diabetic vasculopathy HF is more likely to progress with a preserved ejection fraction. In addition, symptoms of COPD or obesity may overlap with or mask symptoms of HFpEF. The issues of over- and misdiagnosis of HFpEF in primary care are discussed in our review, which emphasizes the nonspecific nature of symptoms, such as breathlessness and leg edema in patients with type 2 diabetes mellitus. It is of utmost importance for healthcare providers to be aware of unusual manifestations of heart failure and, vice versa, of diseases that masquerade as heart failure. This will enable them to manage risks in these patients with greater consistency.

Keywords: heart failure, type 2 diabetes mellitus, case report, misdiagnosis, primary care, transthoracic echocardiogram, natriuretic peptide, COPD, exertional dyspnea, edema

Introduction

Heart failure (HF) and type 2 diabetes mellitus (T2DM) have a high degree of commonality at the vascular level, and are prevalent conditions that frequently co-exist. The presence of T2DM increases the risk of HF, while HF has a significant impact on the vascular outcomes of patients with T2DM.[1] The majority of patients with T2DM meet the criteria for multimorbidity.[2] HF is also a complex phenomenon, with multimorbidity increasing exponentially with age in different phenotypes.[3] In such patients, comorbidity is considered concordant, that is, diseases that share pathophysiological pathways with HF and T2DM; or discordant, that is, conditions whose management and pathophysiology are not directly related to the underlying diseases.[4] These circumstances render the diagnosis of HF challenging. The diagnosis of HF typically commences in primary care, but it can be challenging to diagnose without transthoracic echocardiography (TTE) and assessment of natriuretic peptide levels, particularly in the early stages of the disease, due to the slow

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progression of the disease with only subtle signs or symptoms, leading to a delayed or missed diagnosis and inadequate therapy, including risks management. The following case reports illustrate the over- and under-diagnosis of HF in patients with T2DM in primary care settings:

Case 1

A 62-year-old male patient was referred to the cardiology department because of symptoms of fatigue, progressive exertional dyspnea, and wheezing that was loud enough to hear on his own. The patient was conscious, oriented, and hemodynamically stable, with normal vital signs, including blood pressure of 138/82 mmHg, pulse of 93 bpm, temperature of 36.7°C, normal respiratory rate, and oxygen saturation of 91% on room air. The body mass index was 21.1 kg/m^2, and physical examination revealed wheezing in all lobes of the chest. Physical examination results were otherwise normal, and there was no edema or hepatomegaly.

The patient had a history of T2DM, controlled hypertension, and tobacco use (66 pack-years). Over the past year, the patient experienced reduced exercise tolerance, dyspnea on exertion, and ankle swelling, which were interpreted by primary care physicians as HF stage C according to the American College of Cardiology/American Heart Association (ACC/AHA) and functional class III according to the NYHA classification. The patient had a non-productive cough with a small amount of sputum for a long time in the morning. The patient was treated with Perindopril, Indapamide, Bisoprolol, Spironolactone, Aspirin, and Metformin. The symptoms accelerated within one week prior to admission, with the patient experiencing dyspnea on exertion equivalent to walking <100 m.

The differential diagnoses included acute decompensated HF and chronic obstructive pulmonary disease (COPD). It was unclear whether the patient's progressive exertional dyspnea resulted from single or multiple pathological processes. Progressive COPD could explain the patient's worsening dyspnea, whereas left-sided heart disease may result in similar symptoms.

During hospitalization, the patient had an HbA1c level of 8.7% and NT-proBNP level of 232 pg/mL. A transthoracic echocardiogram (TTE) showed normal chamber size, ventricular function, and pulmonary hypertension with an estimated pulmonary artery systolic pressure of 33 mmHg. Chest computed tomography revealed a normal heart chamber size, pulmonary fibrosis, and pulmonary emphysema. Spirometry results indicated the presence of non-reversible airflow limitation, as evidenced by the FEV_1/FVC ratio of 0.48 pre- and 0.51 post-bronchodilation, FEV_1 was 24% of the predicted value.

The patient's symptoms, including low exercise tolerance, improved with medical management, including β_2-agonist /anticholinergic combinations. No loop diuretics were administered. The patient was discharged after five days.

Therefore, the patient was incorrectly diagnosed with HF during primary care. The presence of hypertension and T2DM placed the patient at risk for HF; however, the absence of structural heart disease indicated that he met the criteria for stage A according to the ACC/AHA stages. It is important to note that the threshold for suspected acute decompensated heart failure, as indicated by the NT-proBNP level, is not 125 pg/mL but rather 300 pg/mL. Dyspnea, a hallmark symptom of COPD, occurs during exertion or physical activity, particularly in the presence of emphysema and may also be present in heart failure. The Modified Medical Research Council (mMRC) Dyspnea Scale, a validated questionnaire, can be used to assess this symptom. In this case, the patient's dyspnea corresponded to mMRC grade 3, as he stopped breathing after walking approximately 100 m. Finally, in heart failure, pulmonary function tests did not detect airflow obstruction, whereas in our patient, the test confirmed COPD with Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 4.

Case 2

A 59-year-old woman visited a primary care facility where her plasma glucose level was extremely high (28.4 mmol/L). As a result, she was referred to the city hospital and admitted on the same day. The patient complained of fatigue, thirst, polyuria, moderate exertional dyspnea, and swelling in her legs. She was conscious and oriented, with vital signs including blood pressure of 125/78 mmHg, pulse of 75 bpm, normal respiratory rate, and oxygen saturation of 95% when exposed to normal air conditions. The body mass index was 34.9 kg/m^2. Pulmonary auscultation indicated the presence of mild bilateral basal crackles, and the patient exhibited peripheral edema covering up to 2/3 of both lower legs.

The patient's medical history included chronic hypertension, T2DM (12-year history and fasting glucose levels of 11–12 mmol/L), obesity, nontoxic goiter with euthyroidism, and mild iron-deficiency anemia. For several years, the patient complained of leg swelling, which was attributed to chronic venous insufficiency (CVI) by primary care physicians owing to its asymmetrical nature (predominantly on the right). The patient was treated with Enalapril, Bisoprolol, rapid-acting insulin, and compression stockings.

Upon admission to the city hospital, blood tests revealed an HbA1c level of 11.6% and NT-proBNP level of 1840 pg/mL. Echocardiography demonstrated a normal left ventricular ejection fraction of 54% but a dilated left atrium of 42 mL/m^2, concentric left ventricular hypertrophy with an LVMI of 143.7 g/m^2, diastolic dysfunction with an E/A ratio of 1.1, and an E/e' ratio of 15. Ultrasonography of the lower-extremity veins revealed no remarkable findings. The initial six-minute walk test (6MWT) distance (6MWTd) was 292 m.

Once the diagnosis of heart failure with preserved ejection fraction (HFpEF) was established, treatment was initiated in accordance with the available clinical guidelines, which included the use of loop diuretics. Following treatment, the patient's symptoms significantly improved, and the six-minute walk test showed notable enhancement, with a substantial 6MWTd increase of 150 m.

As can be seen, the patient's HF was misdiagnosed by primary care physicians. The patient's medical records did not mention the risk of HF (stage A) despite the presence of hypertension and diabetes, which may be due to differences in the approach to classifying the stages of HF in various countries. Leg edema, which can be caused by both heart failure and CVI, poses a diagnostic challenge for primary care physicians. The key to diagnosing our patient was the use of NT-proBNP and TTE, which led to the diagnosis of stage C.

Discussion

The present report of these two cases reinforces the importance of laboratory tests for natriuretic peptides and TTE, which facilitate a straightforward diagnosis. Doctors typically perform these tests when HF leads to hospitalization. However, some signs and symptoms of HF may be overlooked in primary care settings where the diagnosis of HF typically begins (Figure 1).

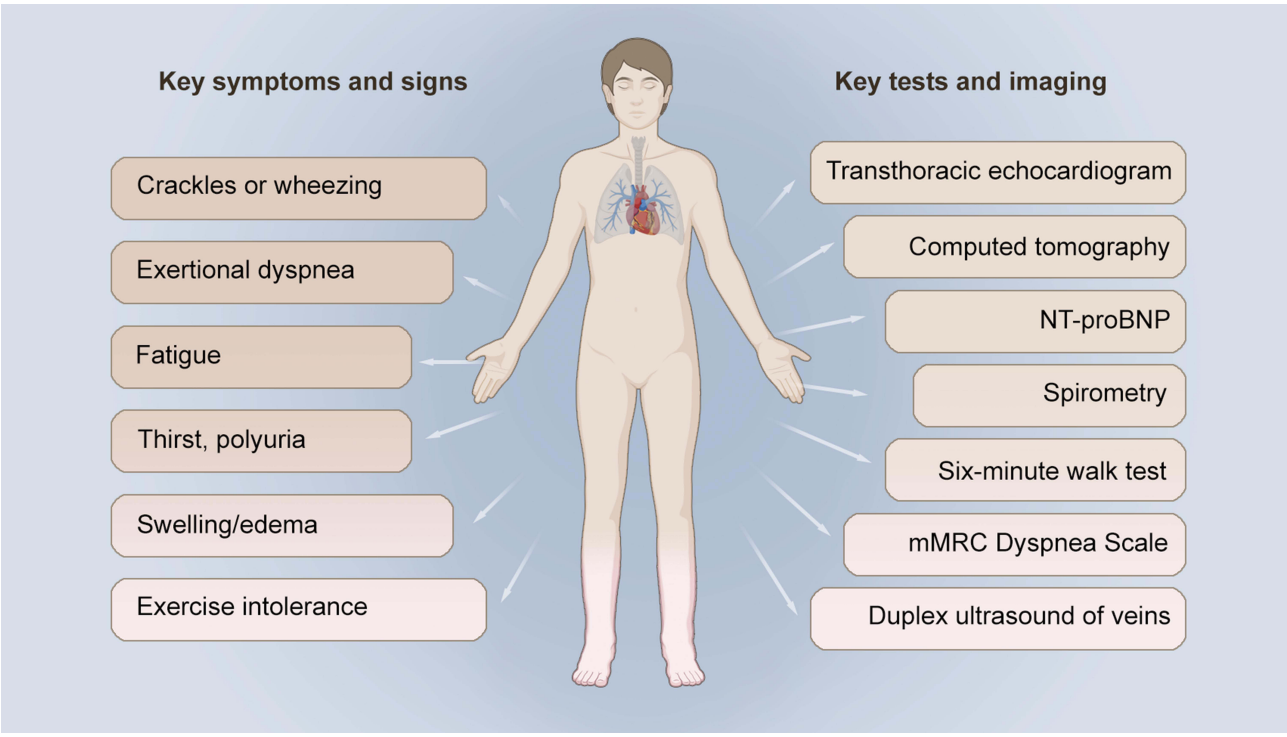

Figure 1 Key symptoms, signs, tests and imaging mentioned in the review. Abbreviations: mMRC, Modified Medical Research Council; NTproBNP, N-terminal prohormone of brain natriuretic peptide.

To improve diagnosis, additional investigations of natriuretic peptides and referrals for TTE have become more common in primary care over the past decade.[5] Primary care physicians usually follow guidelines that recommend TTE for individuals with symptoms and signs suggestive of HF and natriuretic peptide levels above the exclusionary threshold. Nevertheless, this strategy has not been fully implemented, which may result in the misdiagnosis of HF if primary care physicians rely solely on clinical assessments.[6] For instance, they may attribute exercise intolerance and dyspnea to age, deconditioning, or obesity rather than recognizing them as indicators of HF. However, more than one-third of primary care patients labelled with HF may not have HF, and such overdiagnosis may result in inadequate patient management.[5]

Due to diabetic vasculopathy or pan-vasculopathy HF is more likely to progress with a preserved ejection fraction and often occurs without common triggers, such as coronary or valvular heart disease.[7] Meanwhile, it is important to note the incremental diagnostic and prognostic role of strain echocardiographic imaging for identifying individuals with sub-clinical myocardial dysfunction vs those without cardiac damage. Despite preserved left ventricular ejection fraction, myocardial strain parameters can be significantly impaired in heart failure patients and critically illy patients. Strain echocardiographic imaging may be useful in the Emergency Room for a rapid prognostic risk stratification of critically illy patients.[8,9]

HFpEF is a "chameleonic" syndrome with a wide range of clinical manifestations, making it important to rule out other potential diagnoses.[10] This difficulty is particularly relevant in patients with T2DM, where the problem of misdiagnosis of HF in primary care is more pronounced than in patients without T2DM.

Several studies have explored the issues of misdiagnosis and overdiagnosis of HF; however, few have specifically addressed misdiagnosis in patients with T2DM. These studies have identified a number of factors that contribute to the misdiagnosis of HF. Cardiovascular conditions, including hypertension, ischemic or valvular heart disease, and atrial fibrillation, are associated with both undiagnosed and unrecognized HF. These conditions can lead to cardiomyopathy or cardiac dysfunction, which directly contributes to this association. Non-cardiovascular comorbidities such as COPD, renal impairment, cognitive disorders, smoking, and obesity are also associated with undiagnosed or unrecognized HF.[6]

COPD is a common coexisting condition among patients with HF, particularly those with HFpEF. The prevalence of HF in patients with COPD and that of COPD in patients with HF varies significantly. The reported prevalence of HF in COPD patients ranges from 7 to 21%, with higher rates observed when structured and adjudicated HF criteria are employed.[11,12] Similarly, the prevalence of COPD in HF registries ranges from 10 to 40% and is higher when the GOLD criteria for COPD diagnosis are used.[12,13] In HFpEF, the COPD prevalence ranges from 6 to 38% and is higher than that in HF with reduced ejection fraction (HFrEF) in most cohorts that enroll both HF phenotypes.[14] In HF trials, COPD prevalence is lower than that in registries, ranging from 9 to 15%, and is often similar between HFrEF and HFpEF.[13,15] The differences in COPD prevalence across cohorts and between registries and trials may result from specialty bias (pulmonologist or cardiologist), self-reported COPD only, obstructive deficit criterion used (American Thoracic Society/European Respiratory Society or GOLD), and misdiagnosis of HF decompensation as COPD exacerbation.

The exacerbation of COPD can be mistaken for decompensated HF and vice versa, due to the presence of similar signs and symptoms, such as dyspnea, pulmonary crackles or wheezing, exercise intolerance, fatigue, and edema. In HF, these symptoms are manifestations of a structural or functional cardiac abnormality that reduces cardiac output or elevates the intracardiac pressure. However, we must respectfully disagree with the assertion that HF should be considered in any patient presenting with breathlessness and the above signs in primary care, as stated in a recent study.[16] Our case 1 report showed that patients with T2DM and hypertension were only at a risk for HF. Although sensitive (> 80%), these signs and symptoms lack specificity (< 35%) for diagnosing HF.[17]

It is of concern that COPD can mimic or exacerbate underlying HFpEF, where echocardiographic alterations are more subtle than those in HFrEF, and natriuretic peptides concentrations may not distinguish between COPD and HF.[18] It is also important to note that spirometry, a differentiating test, is underutilized in patients with HF and COPD: while more than 80% of these patients undergo TTE only approximately 40% undergo spirometry.[19]

In patients with T2DM, HF is frequently accompanied by swelling, which may be erroneously attributed to dependent edema, CVI, or obesity in obese patients.[20] Lower extremity swelling can have various causes ranging from minor venous valve dysfunction to HF, and can be classified as edema, lymphedema, or lipedema. Lower extremity edema occurs due to excess fluid accumulation in the interstitium. Unilateral edema is typically caused by deep venous

thrombosis,[21] whereas bilateral edema may be caused by HF, pregnancy, medications, and particularly renal failure, which can delay the recognition of underlying or coexisting HF. In order to ascertain the underlying cause of edema, it is helpful to determine whether the edema is unilateral or bilateral.[22] Lymphedema, a progressive condition characterized by lymph fluid accumulation, causes swelling of the extremities and can be classified as primary or secondary. Secondary lymphedema is more common and is attributable to underlying conditions such as infection, trauma, cancer, obesity, and radiation.[23] Lipedema is a bilateral disorder characterized by the accumulation of subcutaneous adipose tissue in the lower extremities. The exact cause of lipedema remains uncertain, but it is believed to have a genetic component and may be related to hormonal changes.[24] A number of diagnostic techniques have been used to differentiate these conditions. Duplex ultrasound is the modality of choice to initially identify lower-extremity edema, such as deep venous thrombosis and venous reflux, due to its high sensitivity and specificity. Other modalities include computed tomography, lymphoscintigraphy, bioimpedance spectroscopy, and magnetic resonance imaging, including lymphangiography. Magnetic resonance imaging is the preferred modality owing to its anatomical and functional diagnostic capabilities. However, ultrasound is a pragmatic alternative when other diagnostic methods are not an option.[25]

It seems presence of obesity is a more likely indicator underlying diastolic dysfunction (and likely accurate HFpEF diagnosis) in T2DM patients. In this regard, a recent systematic review and meta-analysis is noteworthy.[26] The authors found that abnormal fat distribution was significantly associated with the risk of developing cardiac diastolic dysfunction and HFpEF.

In addition to natriuretic peptide tests, TTE, duplex ultrasound, and spirometry, our patients also underwent the 6MWT and were assessed using the mMRC questionnaire. The mMRC is employed in the new GOLD recommendations to categorize the symptomatic burden of COPD, thereby furnishing valuable insights into COPD-induced disability.[27] Interestingly, the 6MWT has been used for over three decades to assess exercise capacity in patients with respiratory diseases and, more recently, in patients with HF.[28,29]

A mild-to-moderate relationship between HF assessed by the NYHA class and the 6MWTd has been demonstrated.[30] This distance is indicative of an individual's exercise tolerance and correlates with both functional capacity and maximal oxygen consumption. The predictive value of the 6MWT can be enhanced by combining it with other variables, such as the cardiac index or left ventricular ejection fraction. When a cardiopulmonary exercise test is unavailable, the 6MWT may provide prognostic information that complements or substitutes for the peak aerobic capacity. For severely impaired patients with advanced HF who cannot undergo a maximal exercise test, the 6MWT may serve as an indicator of maximal exercise capacity.[31] Decreased 6MWT performance has been associated with increased mortality, HF hospitalizations, and nonfatal cardiovascular events in patients with HF.[32] However, only a few older studies reported a lack of prognostic role of 6MWT in patients with HF.[33]

The 6MWT has been widely employed in clinical studies to evaluate the effects of treatment on the functional status of patients with HF, with promising results. It is important to note that some clinical trials assessing the effectiveness of treatments using 6MWT have yielded contradictory results for various established life-saving strategies.[31] Nevertheless, modern medical therapies for patients with HF, such as sacubitril/valsartan treatment, have been associated with improvements in 6MWT.[34]

This is of great importance because misdiagnosis of HF can have severe consequences for patient management, including inappropriate treatment and poor outcomes.[5] Multiple studies have emphasized the importance of correctly diagnosing and understanding the type of HF for effective management. Patients with misdiagnosed HF often receive less medication than needed and experience more comorbidities and poorer prognoses.[35] A recent study found that both polypharmacy and potentially inappropriate treatment, which are associated with increased risks of composite endpoint events such as readmission and mortality, are highly prevalent in elderly patients with HF.[36] Another study showed that inappropriate treatment is linked to poor long-term outcomes even in younger patients with HF. The underuse of vital medications, such as renin-angiotensin-aldosterone system inhibitors, β-blockers, and a combination of sacubitril/valsartan, as well as sodium-glucose transport protein 2 inhibitors, increases the risk of all-cause death in patients with HF, irrespective of diabetes status.[37] Delayed treatment or discontinuation of these medications can result in acute decompensation and hemodynamic deterioration in patients with HF.[38]

Conclusion

The coexistence of HF and T2DM is a complex syndrome that negatively affects patients' quality of life, increases the risk of hospitalization, and increases health care costs. The management and prognosis of patients with HF and T2DM are significantly affected by the coexistence of these conditions. Despite advances in the understanding of the patho-physiological mechanisms of HF burdened with cardiometabolic disorders and the introduction of novel approaches to improve patient outcomes and reduce morbidity and mortality, the coexistence of HF and T2DM is not always adequately recognized (and differentiated, for example, from COPD and obesity) in routine clinical practice, particularly in primary care settings. Accurate diagnosis of HF in patients with T2DM is a significant challenge, particularly in chronic settings, because the symptoms and signs typically associated with HF, such as breathlessness and leg edema, appear to have little clinical utility.

The prompt identification of HF in individuals with T2DM within the primary care setting may have an impact on the selection of glucose lowering/HF medications as well as referral to a cardiologist, testing for natriuretic peptides, and/or TTE. All these interventions have the potential to prevent hospitalization for HF and to improve patient outcomes. Enhanced awareness of the high prevalence of HF and the ways in which it can present differently in patients with T2DM (such as the predominance of the HFpEF phenotype) can assist healthcare providers in consistently diagnosing HF in such patients and, accordingly, in risk management in these patients.

Ethics Approval and Consent for Publication

This study was approved by the local ethics committee of West Kazakhstan Marat Ospanov Medical University. Written and signed consent was obtained from both patients to publish her clinical history. Copies of approval and written consents are available upon reasonable request from the authors.

Disclosure

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