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Fatal New-Onset Congestive Heart Failure Related to Adalimumab Use in a Patient with Relapsing Hidradenitis Suppurativa: A Case Report

Authors' Contribution:

Study Design A
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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Male, 67-year-old
Final Diagnosis: Congestive heart failure
Symptoms: Dyspnea • lower extremity edema • orthopnea • SOB
Medication: —
Clinical Procedure: —
Specialty: Family Medicine

Objective: Challenging differential diagnosis

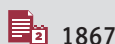
Background: Tumor necrosis factor (TNF)-alpha inhibitors are essential treatments in several inflammatory conditions such as hidradenitis suppurativa (HS). However, they are not without associated risks. In rare cases, new-onset and exacerbations of heart failure have been associated with their use. The purpose of this report is to raise awareness of the need for further study of adalimumab for this adverse effect, as well as to recognize the need for research to find new HS treatment modalities for better care of the broad patient population.

Case Report: We report the case of a 67-year-old man with a history of severe HS and major depressive disorder who came to our hospital complaining of dyspnea, fatigue upon exertion, and lower-extremity edema of 2 weeks' evolution. Symptoms began after the re-initiation of adalimumab for his severe HS. During hospitalization, he was diagnosed with decompensated congestive heart failure (CHF). Extensive studies, looking for ischemic or infectious etiology, yielded negative results. Being aware of adalimumab's potential adverse effects, the team discontinued the medication as a probable cause of his condition. Unfortunately, the patient died secondary to heart failure and septicemia.

Conclusions: The unusual but potentially life-threatening appearance of heart failure secondary to adalimumab use merits thorough attention by primary care doctors and specialists. This adverse event's rare occurrence can underestimate the number of fatalities associated with adalimumab and congestive heart failure.

Keywords: Dermatologic Agents • Drug-Related Side Effects and Adverse Reactions • Education • Heart Failure • Hidradenitis Suppurativa • Physicians, Primary Care

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Background

Hidradenitis suppurativa (HS) is a chronic inflammatory disorder of the pilosebaceous unit, commonly found in intertriginous areas, such as the axilla, inframammary area, and anogenital region. The inflammation is associated with deep, painful subcutaneous nodules, cysts, and abscesses. These lesions may form sinus tracts containing malodorous mucopurulent discharge. The constant inflammation in these areas has long-term consequences such as scarring, chronic pain, skin contractures, and possible disfigurement. Its pathophysiology is not well understood and is thought to be multifactorial. Studies have shown a mixture of components like genetic susceptibility, autoimmunity, hormonal dysregulation, and environmental factors such as smoking and obesity [1]. The trigger is thought to be the constant repetition of microtrauma from microbial factors that activate the innate immune system's pro-inflammatory response [2]. Elevation of pro-inflammatory cytokines such as interleukin (IL) 1-beta, IL-17, and IL-23, as well as tumor necrosis factor (TNF) alpha, have been found on HS lesions, suggesting a dysregulation of the body's adaptive immune response.

TNF-alpha also affects many other tissues, such as its widely studied effect on the myocardium. The pro-inflammatory cytokine alters the beta-adrenergic receptors in the myocardium, depressing cardiac inotropy. This leads to further inflammation and cardiac injury, ultimately producing congestive heart failure (CHF). Despite the evidence associating TNF-alpha with heart failure, inhibition of the cytokine has not achieved significant success. Reports have found that it worsens cardiovascular symptoms, leading to de novo or exacerbations of existing congestive heart failure [3]. Adalimumab, a TNF-alpha inhibitor, is the only FDA-approved biologic treatment for HS. In this case report, we present the case of a middle-aged man with severe HS treated with adalimumab who developed de novo CHF. We want to raise awareness of the potential adverse effects of HS treatment, specifically use of adalimumab. More investigation is warranted to further understand the pathophysiology and improve treatment.

Case Report

We report the case of a 67-year-old man who presented to the services of Manatí Medical Center with a chief complaint of fatigue upon exertion, dyspnea, and lower-extremity edema that had been progressively worsening for 2 weeks. His medical history was significant for a 30-year history of hidradenitis suppurativa (HS) Hurley stage III, hypertension, major depressive disorder, and a positive Mantoux test, treated with isoniazid 12 years ago. On physical exam, he was hypotensive, tachycardic, and tachypneic. On auscultation, a mild holosystolic

murmur with S3 gallop was heard at the apex. Crackles and rales were appreciated in all lung fields, as well as bilateral lower-extremity edema. Additionally, there was mild ascites without abdominal tenderness or guarding. The patient was not confused at any point during history taking or physical exam.

Troponin levels remained constant at less than 0.015 ng/mL, CK-MB less than 1.00 mg/mL, and total creatinine kinase at 15 IU/L, all within normal limits. However, Pro-B natriuretic peptide was elevated at 77 660 pg/mL (normal levels are 5-125 pg/mL). The electrocardiogram showed sinus rhythm with no indication of acute ischemic changes or arrhythmia. A chest X-ray showed marked Kerley B lines, enlarged cardiac silhouette, and bilateral pleural effusion, suggesting exacerbated congestive heart failure. He was admitted to the hospital the same day for clinical stabilization and further treatment.

During the hospital stay, various studies were performed to find the etiology of his CHF. The patient's echocardiogram showed an ejection fraction (EF) of 20-25%, significantly different from a previous study done 2 months ago, which reported an EF of 50%, which also mentioned findings of global hypokinesia of the left ventricle with enlarged atria, left worse than right, and present mitral regurgitation. There were no changes indicating possible myocarditis or pericarditis. Findings of this study suggested new-onset decompensated congestive heart failure (CHF). Other diagnostic tools looking for ischemic and infectious etiology yielded negative results.

A chest CT scan without contrast showed bilateral pleural effusions with bibasilar compressive atelectasis and no evidence of pulmonary or infectious processes. There was also no evidence of an intra-abdominal emergent process on abdominal imaging. The patient did not have significant leukocytosis, with negative blood cultures and pleural fluid culture, suggesting there was no systemic infection or sepsis that may have caused the heart failure. The patient had no coronary disease or cardiovascular risk factors that could explain his symptoms' severity and rapid progression. However, his clinical history revealed that he was re-initiated on adalimumab 2 months before this presentation. Therefore, adalimumab was discontinued as a precaution of potential cause, with an adverse drug reaction probability of 5.

Further investigation with his dermatologist revealed he first started adalimumab treatment 3 years ago with the standard HS regimen, beginning with subcutaneous 160 mg on the first day, and 80 mg on day 15. On day 29 and weekly thereafter, the dose was maintained at 40 mg. After 2 years of utilizing the medication with no complications, it was discontinued due to his lesions' progression. However, even with alternate standard treatments and procedures, his condition had not stabilized. After various hospital admissions, adalimumab was

re-initiated with the standard-dose regimen, as previously described. Once adalimumab was discontinued during this hospital stay, his health continued to decline, with worsening of symptoms. Unfortunately, the patient's condition continued to worsen, increasing his hospital visits for symptom management. On the 8th day of hospitalization, he died due to decompensated heart failure and septicemia.

Discussion

We report a case of new-acute onset CHF in a patient with severe HS who recently re-initiated adalimumab. Although not fully understood, there have been studies describing this adverse effect of TNF-alpha inhibitors. Initially, in various in vitro studies involving mice cardiac myocytes, it was reported that TNF-alpha inhibitors could improve CHF symptoms by reducing the inflammatory response. In practice, this would attenuate ventricular remodeling, fibrosis, and continuous cardiomyocyte apoptosis. However, there are no in vivo data that support these results [3]. A well-known clinical trial investigating the effects of TNF-inhibitors, specifically infliximab, against class III-IV heart failure was prematurely halted, concluding there was an increase in hospitalizations and deaths with a high infliximab dose of 10 mg/kg. At the lower dose of 5 mg/kg, there was no evident benefit or relief of patients' cardiac symptoms [4]. As a matter of fact, most of the cases reporting CHF as an adverse effect of TNF-inhibitors have been with long-term use well after the end of the trial.

In 2003, post-marketing reports from the FDA MedWatch system warned of an alarming rise of new and exacerbating CHF cases in patients stable on TNF-inhibitors for rheumatoid arthritis (RA) [5]. The data included patients on infliximab, etanercept, and adalimumab. Although RA increases cardiovascular risk and most of the patients had comorbid conditions, TNF-inhibitors presented an additive risk factor for the disease. Adalimumab itself had the least cases of CHF reported. The incidence of new cases among RA patients was 0.1%, which was comparable to the placebo group. The patient presented in our case report had an adverse drug reaction probability score of 5, which indicates the adverse effect was a probable effect of adalimumab. This score takes into consideration the timing of symptom onset after medication, literature describing the adverse effect, and exclusion of other possible causes known to cause the adverse effect [6].

While there are studies of TNF-inhibitors warning about new or exacerbated CHF, adalimumab specifically has not been extensively studied for this adverse effect. In 2012, a sizable long-term safety analysis regarding adalimumab on patients with systemic inflammatory diseases demonstrated 0.2 per 100 patient-years of serious CHF events [7]. It should be noted that the

progression and outcome of the disease was not mentioned in their analysis. In the Cochrane review, a meta-analysis on adverse effects of biologics, there was no statistical significance regarding CHF due to TNF-inhibitors, as there was insufficient data and inconsistent definitions regarding the disease [8]. While the literature suggests it is an unusual risk, there has yet to be a meta-analysis discussing risk factors such as dosage, length of time, or re-initiation after a prolonged period leading to CHF occurrence.

With very few options for HS management, it is imperative to understand the relationship between TNF-inhibitors and cardiac myocytes. As previously stated, HS is known to be a systemic inflammatory condition with recorded elevated inflammatory cytokines, including interleukin (IL) 1-beta, IL-17, and IL-23, as well as tumor necrosis factor (TNF) alpha. This continuous inflammatory process leads to known comorbidities such as obesity and diabetes. As HS progresses, the comorbidity burden increases. A retrospective matched cohort study enrolled 5357 patients with mild and severe HS to learn what other conditions HS patients were more likely to develop. The study found that HS patients were 3 times more likely to develop inflammatory conditions compared to individuals without HS. In addition, individuals with severe forms of HS were found to have a 2-fold higher prevalence of metabolic and cardiovascular dysregulations, including congestive heart failure, compared to HS-free individuals. CHF developed in 2.9% of individuals with severe HS and in only 0.5% of HS-free individuals, regardless of treatment. While the data presented showed a comorbidity burden related to HS progression, the results were limited due to small sample size and inconsistent characterization of HS severity. Additionally, the study did not determine whether heart failure development was due to modifiable risk factors or due to the innate inflammatory cardiac damage [9].

As previously mentioned, there has been little research on HS compared to other cutaneous dermatoses. Overall, federal funding for HS in comparison with other inflammatory conditions has been minimal. In 2018, there were only 17 clinical trials dedicated to HS, with even less investigation of model therapies and possible adverse effects [10]. New treatment modalities for HS need to be investigated, as there is a lack of options for a broad patient population with various comorbid conditions. When caring for an individual with HS, awareness of medication effects is not the only way to ensure optimal care. Impairment of quality of life in individuals with HS leads to suboptimal psychological well-being [11]. In a recent meta-analysis, the prevalence of depression in patients with HS was 16.9%. These alarming facts need to be communicated to their primary care providers for prompt recognition of symptoms and urgent management. This intervention will also ensure optimal care.

Conclusions

Management of hidradenitis suppurativa is challenging, and a multimodality approach is usually required. With few treatment options, adalimumab is the only FDA-approved treatment efficacious enough for severe cases of HS. This report presents a fatal case of new-onset acute CHF in an individual re-initiated on adalimumab for severe HS. Understanding the mechanism of action of TNF-inhibitors and cardiovascular decline may help us prevent such cases. Moreover, awareness of CHF as an adverse effect of adalimumab is of utmost importance in primary care to prevent disease progression and fatalities. In addition, understanding the secondary complications of HS such as depression and anxiety will also improve care quality. Management of HS needs to consider many factors for it to be comprehensive and effective. More targeted research regarding new HS treatments is imperative to care for this disease's broad population.

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Conflict of Interest

None.