Information about a real patient is presented in stages (boldface type) to expert clinicians (Dr Beckman), who respond to the information, sharing their reasoning with the reader (regular type). A discussion by the authors follows.

Patient presentation: An 89-year-old woman presents to cardiology clinic with the concern of recurrent shortness of breath and dyspnea on exertion during the previous 6 months. Her symptoms are progressive such that she can no longer walk >10 feet before becoming symptomatic. Previously, she was independent at home and able to climb stairs with groceries or laundry without difficulty. The patient reports dependent lower extremity edema, orthopnea, and paroxysmal nocturnal dyspnea, but neither chest pain, palpitations, diaphoresis, nor lightheadedness. Her medical history is significant for diabetes mellitus, hypertension, hyperlipidemia, and glaucoma. Her medications include insulin, lisinopril, losartan, furosemide, and pravastatin. She has no known medication allergies.

The patient's most recent medical history is notable for a new diagnosis of aortic stenosis now repaired by transcatheter valve replacement (TAVR). She underwent successful valve replacement; however, her hospital and immediate outpatient course were complicated by profound hyperglycemia requiring escalating doses of insulin and readmission to a local hospital. Furthermore, the patient's dyspnea did not change appreciably after valve replacement, and she was hospitalized twice more with acute on chronic heart failure requiring intravenous diuresis. Before discharge, she was started on high doses of oral furosemide. Ongoing symptoms of heart failure despite TAVR prompted her primary care physician to refer her to a cardiologist at a tertiary care center.

The patient's initial examination showed an elderly appearing woman, sitting comfortably in a wheelchair with her son at her side. Her vitals in the office revealed a heart rate of 91 and blood pressure of 135/77. The patient's head and neck examination showed a jugular venous pressure elevated to 12 cm. Cardiovascular examination revealed a regular rate and rhythm with a soft II/VI systolic ejection murmur, normal S1 and S2 with an S3, and nondisplaced point of maximal impact. No sternal heave was appreciated. Examination of her extremities showed bilateral lower extremity 2+ pitting edema. She had good breath sounds bilaterally with rales at both bases but without wheezing.

Dr Beckman: An 89-year-old woman presents with dyspnea with exertion. This is a common concern among elderly patients, particularly those with a history of cardiovascular risk factors including hypertension, hyperlipidemia, family history of heart disease, tobacco use, and obesity. Among the broad causes of dyspnea in this age group, such as obstructive lung disease, anemia, and thyroid disease, car-
diogenic etiologies are common and include heart failure with either preserved or reduced ejection fraction, valvular heart disease (typically aortic or mitral), or ischemic heart disease. In this particular case, the patient presented with dyspnea that was initially thought to be associated with a new diagnosis of severe aortic stenosis.

Class I indications for aortic valve replacement include symptomatic severe aortic stenosis, asymptomatic aortic stenosis with evidence of declining systolic function, or severe aortic stenosis and undergoing cardiac surgery, including coronary artery bypass grafting. This patient presented with symptomatic aortic stenosis and impaired systolic function, as well, both indications for replacement. Given her advanced age and comorbidities, her primary team chose to proceed with TAVR, which is an alternative to surgical replacement in patients who have a prohibitive risk for proceeding with surgery. TAVR may also be considered in patients with high surgical risk and estimated survival of at least 12 months.

Despite appropriate valve replacement, the patient’s symptoms did not improve. A higher index of suspicion should now be placed on the patient’s known impaired systolic heart failure as the cause of her symptoms, in the absence of a benefit from the TAVR.

**Patient presentation (continued):** Our initial assessment was that the patient was grossly volume overloaded with clinical signs of acute on chronic systolic heart failure. We arranged for her to be admitted to the cardiovascular inpatient service for additional intravenous diuresis and obtained previous studies from her outside providers, including coronary angiography, pre- and post-TAVR transthoracic echocardiograms, and intraoperative transesophageal echocardiogram (Figures 1 and 2). These studies were notable for an initial ejection fraction of 30% to 35% with a mean and peak gradient of 34 and 52 mm Hg, respectively, and a calculated valve area of 0.5 cm². Dobutamine stress echocardiography increased her mean and peak gradients to 37 and 83 mm Hg, respectively, with a revised calculated valve area of 0.8 cm². Catheterization revealed nonobstructive coronary artery disease, but the valve was not crossed. Her post-TAVR echocardiogram was unchanged with the exception of a new prosthetic aortic valve associated with trace aortic regurgitation. During the course of her hospitalization, she underwent diuresis of ~20 pounds and was discharged to home.

The patient returned 2 weeks later for posthospitalization follow-up with recurrent dyspnea and weight gain. During the next 6 weeks, the patient was seen in the office 3 more times. Her diuretic regimen was calibrated carefully, adding metolazone to improve diuresis and potassium supplements to avoid hypokalemia. Metolazone dosing was implemented by using a weight-based protocol to avoid hypotension and volume overload. After 2 months, the patient reached a stable stage of euvolemia, was no longer dyspneic when recumbent, and had no evidence of volume overload on examination. Despite successful volume management, however, she returned to the office still feeling poorly. She reported a feeling of malaise, chronic aching, chronic fatigue with the need to nap in the afternoon, and the sense that, despite improved volume management and significantly reduced dyspnea, she remained without energy.
Because aggressive heart failure therapy failed to resolve most of her concerns, we took a step back to re-review the patient's course and primary data to investigate additional possibilities to explain her symptoms. In questioning the circumstances around her fatigue and need for an afternoon nap, she reported poor sleep with frequent waking, and her son noted that she was known to snore. A sleep study was recommended to evaluate for obstructive sleep apnea, but the patient refused. Furthermore, her joints ached and were stiff, although there was neither redness nor swelling. She also chronically felt warm and perspired. We performed a detailed examination and found that this 5 foot 4 inch woman had hands the same size as her 6 foot 3 inch physician and that her facial features were far coarser than her son's, including frontal bossing and enlarged tongue (Figure 3). A detailed review of systems revealed that the patient required mechanical removal of her wedding ring when she could no longer slide it off her finger. A request for previous photographs showed that her unique facial features had developed later in life.

Dr Beckman: An additional diagnosis causing fatigue and poor sleep underlying the patient's current symptoms could only be revealed once more common diagnoses, in this case aortic stenosis and systolic heart failure, were safely eliminated. Her outpatient providers successfully managed the patient's heart failure, but her symptoms persisted; thus, it became appropriate to consider alternate explanations for ongoing symptomatology. This patient has a constellation of symptoms including systolic heart failure, diabetes mellitus, sleep apnea, joint stiffness, heat intolerance, and coarse physical features. Of this symptom complex, in older patients, most of these are common and unremarkable. Heart failure, sleep apnea, and joint stiffness, in particular, can accompany infiltrative processes, including senile amyloid. However, the patient's facial features were distinctly coarser than her son's and her hands were very large for a woman of her size, which would not be expected in amyloid. Once a constellation of these symptoms and signs is organized, the patient needs to be evaluated for acromegaly.

Patient presentation (continued): Laboratory testing confirmed the diagnosis of acromegaly with significantly elevated serum levels of growth hormone (29 ng/mL; normal, 0–3 ng/mL) and insulin-like growth factor (768 ng/mL; normal,
33–179 ng/mL). Brain MRI showed the presence of a pituitary adenoma, the likely source of excess growth hormone (Figure 4).

After diagnosis, the patient was referred to a neuroendocrinology clinic. Consideration was made for surgical resection; however, given her advanced age and high-risk surgical candidacy, medical therapy was prescribed. She was started on 90 mg of lanreotide, a somatostatin analogue, which she received subcutaneously once a month. Within 2 months, her serum levels of insulin-like growth factor had dropped to 344 ng/mL, and her levels of growth hormone were normal (2 ng/mL). She had some intermittent diarrhea, a known side effect of lanreotide, which resolved after decreasing her dose to 60 mg monthly. Otherwise, she had dramatic improvement in her shortness of breath and exertional dyspnea. After 4 months of therapy, she required neither insulin nor diuretic. Moreover, her snoring diminished, her sleep quality improved, her achiness resolved, and her fatigue reduced. Notably, repeat echocardiography revealed an unchanged ejection fraction of 30% to 35%.

**DISCUSSION**

We present a patient who had clinical signs and symptoms of refractory decompensated heart failure, eventually found to have a late presentation of acromegaly with dramatic response to medical therapy. This case illustrates the importance of careful physical examination, and reviewing common causes of diagnostic bias, as well, when evaluating patients that present from outside institutions.

Acromegaly is a rare, pathologic overproduction of serum growth hormone, typically the result of proliferation of somatotrophs within the anterior pituitary. The estimated yearly incidence is between 3 and 4 cases per million people per year, and the average age of diagnosis is 40 to 45 years. Our report of an 89-year-old woman is the second oldest case to be published in the literature.

The signs and symptoms of acromegaly are a direct response of a neuroendocrine imbalance. Excess growth hormone stimulates receptors in the liver and cartilage, which leads to the clinical manifestations of acromegaly including soft-tissue swelling, arthralgias, jaw prognathism, hyperglycemia, hypertension, and occasionally, respiratory and cardiac failure. This case demonstrates that acromegaly is a known, although not often recognized, etiology of systolic heart failure.

Years of excess growth hormone lead to substantial cardiovascular changes, including cardiomegaly, ventricular hypertrophy, fibrosis, and eventually cardiomyocyte degeneration. Additionally, there are known vascular effects, although it is not thought that this leads to an increased risk for coronary artery disease. The coexistence of other diseases, including diabetes mellitus, hypertension, or thyrotoxicosis, further exacerbates cardiovascular disease, particularly cardiomyopathy. Thus, patients with acromegaly have increased morbidity and mortality primarily because of the end-organ effects of excessive growth hormone.

Although not as prevalent in the literature, valvular disease as a result of long-standing acromegaly has been described. Initial reports showed that mitral and aortic abnormalities were present in 19% of patients at the time of autopsy. A more recent study showed a much higher prevalence of valve disease in both active and
cured acromegaly patients, up to 86% versus 24% in age-matched controls. Interestingly, acromegaly was associated with a greater proportion of regurgitant valvular heart disease. This may be attributable, in part, to dilated aortic roots often associated with acromegaly. Notably, our patient presented with primarily aortic stenosis; however, she did have an element of mitral regurgitation, likely from dilation of her ventricle.

Treatment of acromegaly, whether surgical or pharmacological, can reverse many of the cardiac structural changes of excessive growth hormone. Our patient exhibited a number of cardiovascular complications, including ventricular hypertrophy, systolic dysfunction, and valvular disease. She also had other symptoms of acromegaly including enlarged features and visual field deficits, although these were not as pressing as her cardiovascular concerns. Only after a careful reexamination of all the available data was the final diagnosis made.

CONCLUSION

This case began with an elderly woman who had presented to cardiology with a common concern found in many ambulatory clinics: shortness of breath. She had likely experienced the effects of acromegaly for years before receiving her diagnosis. Her impressive response to corresponding medical therapy shows that careful consideration should always be made when standard therapy fails in patients for presumed diagnoses. This case reinforces the need for deliberate and detailed physical examination, the value of carefully reviewing primary data, and the necessity to avoid cognitive bias when evaluating patients for the first time.

DISCLOSURES

None.

AFFILIATIONS

From Department of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA (A.P.K.); and Department of Vascular Medicine, Vanderbilt University Medical Center, Nashville, TN (J.A.B.).

FOOTNOTES

Circulation is available at http://circ.ahajournals.org.

REFERENCES

Larger Than Life: A Unique Cause of Dyspnea in an Elderly Woman
Aaron P. Kithcart and Joshua A. Beckman

Circulation. 2016;134:689-693
doi: 10.1161/CIRCULATIONAHA.116.023169

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/134/9/689

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/