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Not all wheezing is COPD

All that wheezes…

A clue to HIV infection

Median arcuate ligament syndrome:
- Incidental or real?
- A clinical dilemma
- When to hunt for zebras

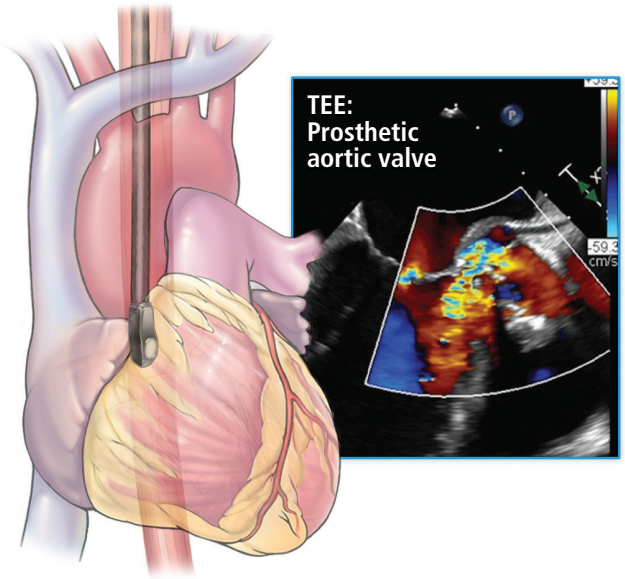
Parsonage-Turner syndrome

Vaccinations in pregnancy: Flu, Tdap, COVID-19

Male and female pattern hair loss

Managing cancer pain: Frequently asked questions

Imaging in suspected infective endocarditis



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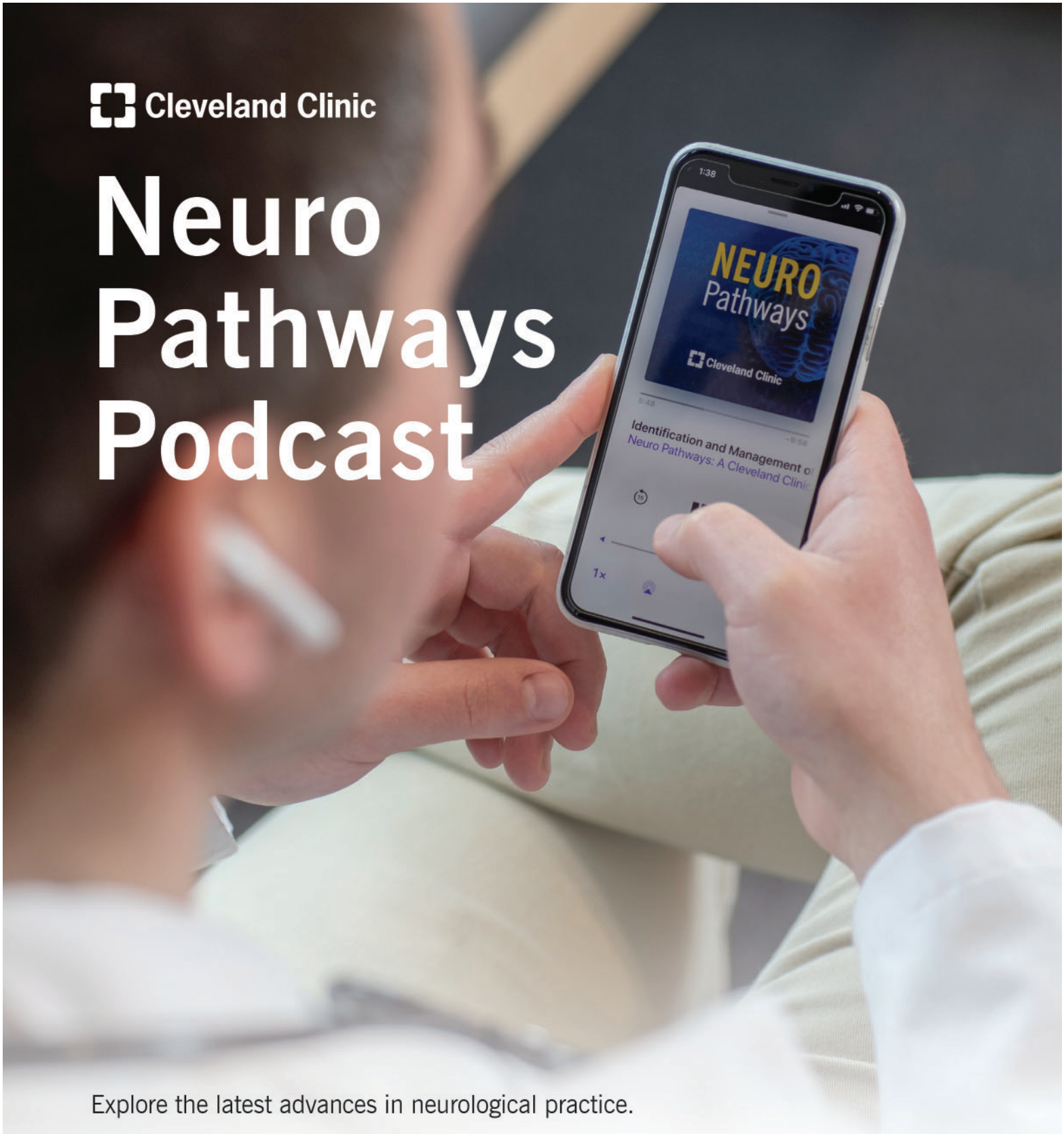

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Awareness can prompt the search for clinical zebras

I recently read a book of personal reflections on approaching patient care by Roger Cass, an experienced internist/rheumatologist, *Diagnosis: Clinical Skills In Medicine*.[1] On the heels of that, reading the short paper by Mandzhieva et al[2] and the commentary by Rodriguez[3] in this issue of the *Journal* on the median arcuate ligament syndrome (MALS) prompted me to consider the process by which I evaluate patients with certain symptoms. What distinguishes insightful quick diagnosis from premature closure (other than that the diagnosis turns out to be incorrect in the latter)?

As a rheumatologist, I am frequently consulted in the hospital to evaluate acutely ill patients who have a panoply of symptoms, laboratory findings, and sometimes physical examination findings extending across several organ systems. By the time we are asked to see these patients, we are often starting way down the differential diagnosis list, seriously considering the unusual if not the outright arcane possibilities. We are asked to look for the zebras. But that is not usually the case for patients ultimately diagnosed with MALS and others who experience common, regionally localized pain symptoms at their initial presentation to physicians.

As exemplified by the patient described by Mandzhieva et al,[2] patients present to us every day with common and seemingly simple "complaints." At what point do we start to look for zebras when we are hearing familiar hoofbeats? Or for that matter, when do we start expending a patient's time, money, and sometimes anxiety on efforts to prove those hoofbeats are indeed from horses? We likely all have slightly different philosophic approaches in making these decisions, and our individual thresholds will vary based on the situation: specific patient needs, time pressures in the office, referring physician, and our anecdotal memory of recent similar patients, which introduce bias to our clinical analysis.

After this past week, when I was seeing patients in clinic with internal medicine residents, I reflected on why I had pontificated the way I did on the specific use and avoidance of testing for less common entities. In a rheumatology clinic, testing decisions invariably involve serologies, for which my mantra is that the specific clinical history and physical examination should dictate specific serologic testing, and panserologic testing should not be obtained to divine the diagnosis. What specific experiences have led me to this relative testing nihilism compared with some of my highly skilled colleagues? I am not sure.

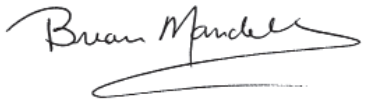
What of the patient discussed here,[2] who had abdominal pain, normal basic laboratory tests, and a minimally suggestive examination? As I read the clinical presentation, I wondered at what point I would have embarked on an aggressive diagnostic approach. The history is truncated, but I am sure the decision to embark on a series of initially focused tests was influenced by the "vibe" the physicians received from the patient (much tougher to glean from a virtual visit in this age of COVID-19). Perhaps the decision was driven by the recognition of chronicity of related symptoms, or that this specific clinical event was far more severe than what was anticipated from reflux

doi:10.3949/ccjm.88b.03021

alone, or that the symptoms didn't respond to treatment as anticipated. The ultimate suspected diagnosis attained from imaging was not likely anticipated.

It is not certain whether the pain associated with MALS is of vascular or neurogenic origin, or both.[3] Several other syndromes can present with intermittent abdominal pain from intermittent gut ischemia. Once atherosclerotic and thromboembolic causes are believed to be less likely, diagnostic considerations are dominated by uncommon conditions. In my clinic, vasculitic syndromes are the initial ones we try to confirm or exclude, and this invariably involves vascular imaging. Although imaging provides far more direct information than serologies, the results are not always straightforward. The pattern of findings (stenoses, aneurysms, or dissections), in the context of the clinical history and examination, helps to distinguish atherosclerosis and vasculitis from their mimics.[4,5] As Rodriguez points out, diagnosing the uncommon requires "meticulous evaluation to rule out more common pathology."[3]

Circling back to my original effort to understand what prompts me, or any clinician, to look hard for the uncommon causes of common symptoms, it seems to be the gestalt that speaks to some part of the total patient presentation that doesn't quite fit the expected. The relative value of this gestalt stems from the breadth of our personal experience, which is always limited. We may not all be confronted on a daily basis with the specific challenge of deciding whether to treat a patient for MALS. But reading about this and other less common syndromes contributes to our warehoused cognitive experience and, hopefully, provides impetus for a bit of extra reflection before offering up our diagnosis.



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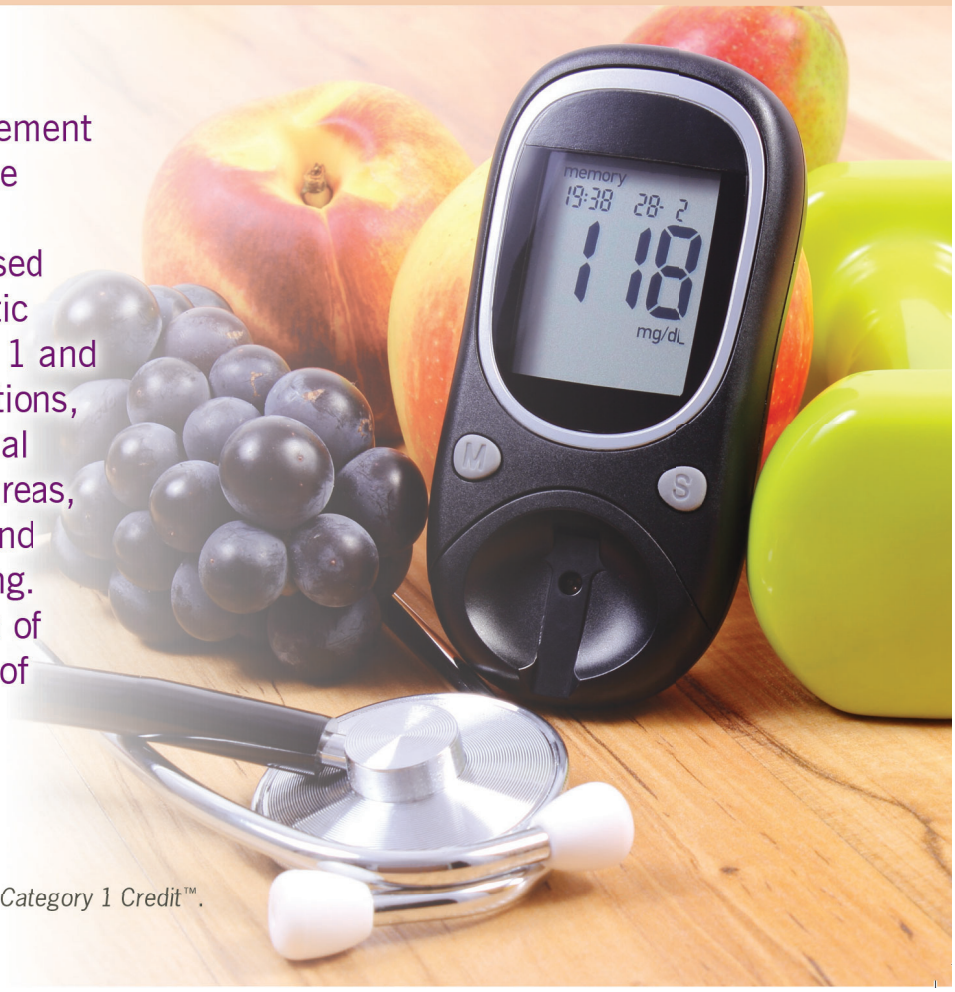

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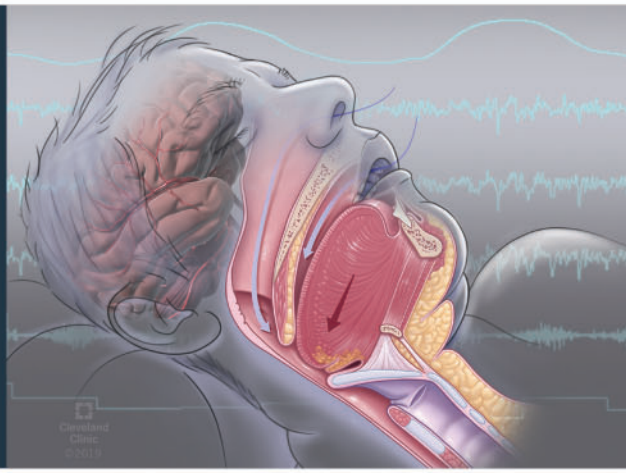

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Median arcuate ligament syndrome: Incidental finding or real problem?

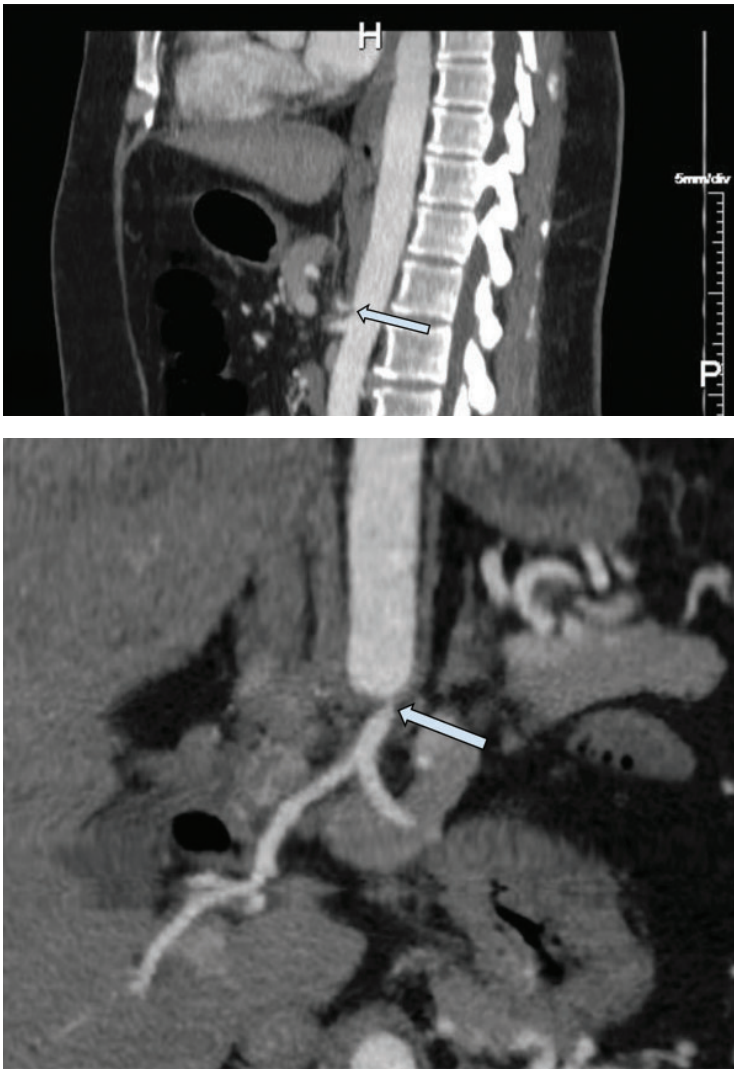

Figure 1. Contrast-enhanced computed tomographic angiography, sagittal (top) and 3-D coronal (bottom) views, showed severe stenosis at the origin of the celiac artery (arrow) with associated soft-tissue attenuation, suggestive of median arcuate ligament syndrome.

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A 43-year-old woman was admitted with pain in the epigastrium and right upper quadrant that radiated to the back and was associated with nausea and dry heaves. The pain had started suddenly 5 days previously. She described it as burning, pressure-like, and intermittent without any relation to meals. She had no vomiting, fevers, chills, change in bowel habits, or unintended recent weight loss. She had a history of chronic gastroesophageal reflux disease and had multiple episodes of this epigastric pain over the past few years, but she always thought it was related to her reflux, and it was never this severe. She had never undergone upper endoscopy.

See related editorial, page 143

On physical examination, she had mild tenderness to palpation in the epigastric area. Laboratory studies were essentially normal.

Right upper quadrant ultrasonography showed an unremarkable gallbladder and biliary tree. Computed tomography (CT) of the abdomen revealed compression of the celiac artery by the arcuate ligament. She subsequently underwent CT angiography of the abdomen, which showed severe stenosis of the origin of the celiac artery with associated soft-tissue attenuation, suggestive of median arcuate ligament syndrome (MALS) (**Figure 1**). The celiac artery beyond the area of narrowing was widely patent. There were prominent arterial collaterals in the peripancreatic region, with some prominence of the gastroduodenal artery likely related to contribution to the celiac distribution from the superior mesenteric artery (**Figure 2**). The superior mesenteric artery and inferior mesenteric artery were widely patent with no radiographic evidence of bowel ischemia.

It was not clear if her symptoms were related to artery compression or to a severe form of gastritis or peptic ulcer disease, with MALS as an incidental finding. She was subsequently evaluated by a gastroenterologist and a general surgeon for possible laparoscopic release of the ligament.

The patient's symptoms were not typical for MALS; they were new in onset and she had no weight loss, no abdominal pain after eating, and no food aversion. The surgeon did not attribute her abdominal pain to MALS and did not recommend surgery.

The gastroenterologist recommended upper endoscopy, which showed no acute pathology to explain her symptoms, and biopsy studies were negative.

Her symptoms improved during her hospital stay, and she was counseled to follow up with her primary care physician for further testing if required.

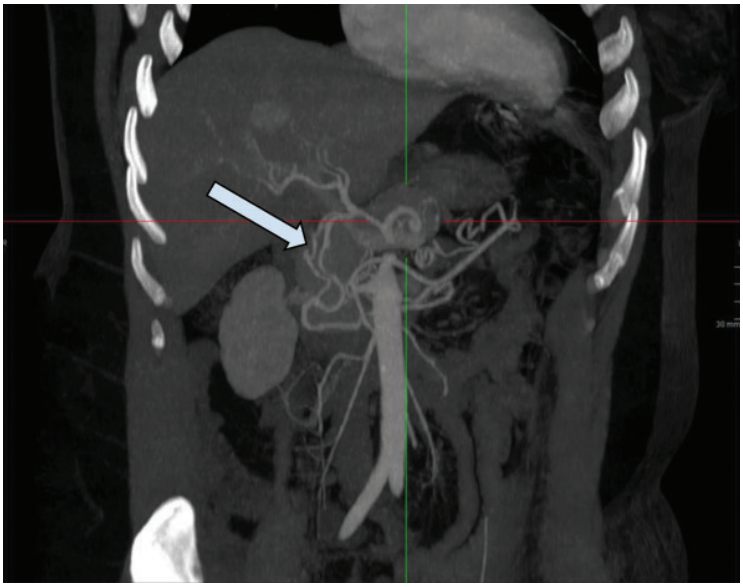

Figure 2. Contrast-enhanced computed tomographic angiography showed prominent poststenotic arterial collaterals in the peripancreatic region (arrow), with prominence of the gastroduodenal artery related to contribution to the celiac distribution from the superior mesenteric artery, which indicates the stenosis is chronic and hemodynamically significant.

THE CLINICAL PICTURE OF MALS

The median arcuate ligament is a fibrous arch connecting the crura of the diaphragm forming the aortic hiatus and lying superior to the celiac artery. MALS, also known as Dunbar syndrome or celiac artery compression syndrome, is a rare phenomenon caused by extrinsic compression of the celiac trunk by the median arcuate ligament.

Women with MALS outnumber men by 2:1 to 3:1, and the typical age of onset is in the fourth and fifth decades.[1] Often, history and physical findings are nonspecific. The most common clinical manifestation is chronic epigastric abdominal pain, most of the time postprandial or exercise-induced. Other symptoms include nausea, emesis, bloating, weight loss, and fear of the pain triggered by eating, leading to food avoidance. Physical examination may reveal epigastric tenderness or a bruit that is amplified with expiration, but these are nonspecific.

What causes the epigastric pain?

Theories regarding the pathophysiology of epigastric pain associated with MALS include foregut ischemia due to compressed celiac artery, midgut ischemia due to vascular steal syndrome, and overstimulation of the celiac plexus with subsequent splanchnic vasoconstriction and ischemia. Recently, ideas about the etiology of MALS have shifted from its being a vascular disease to a neurogenic disorder with compression of the surrounding celiac plexus and ganglion.[2]

The patient's symptoms were not typical for MALS; they were new in onset, and she had no weight loss or abdominal pain after eating

Mimics of MALS

MALS resembles several other abdominal disorders in its symptoms, posing a diagnostic challenge for the clinician. It can be mistaken for gastroparesis, gastritis, peptic ulcer disease, hepatitis, cholecystitis, biliary dyskinesia, appendicitis, chronic pancreatitis, colorectal malignancy, or chronic mesenteric ischemia secondary to atherosclerotic disease. Most patients undergo an extensive workup for other diagnoses with abdominal ultrasonography, abdominal CT, upper endoscopy, and hepatobiliary iminodiacetic acid scanning.

MALS is considered a diagnosis of exclusion, and it can coexist with other intra-abdominal pathologies and be a confounding factor.

CT angiography, magnetic resonance angiography, and duplex abdominal ultrasonography during inspiration and deep expiration are the most common diagnostic studies for

MALS. The increasing use of CT in the assessment of abdominal pain has led to more frequent diagnosis of MALS.

Also, many patients who have no symptoms exhibit radiographic evidence of celiac compression, and mild compression can normally be seen during expiratory-phase CT angiography; inspiratory imaging can confirm that the narrowing is real. Petnys et al[3] showed that 3% of patients without symptoms have celiac artery compression on CT angiography. In a retrospective study, Heo et al[4] showed that 87% of patients with MALS had no symptoms, and the condition was incidentally diagnosed by CT. Anatomically, up to 24% of the population may have compression of the celiac artery; however, fewer than 1% of them have symptoms.[5]

To enhance the benefit of surgical intervention, studies aimed at improving the ability to reliably diagnose MALS are required. Surgery should be reserved for patients who would benefit from it, and patient selection continues to be challenging, as there is relatively poor correlation between the radiographic findings of celiac artery compression and the presence or severity of symptoms. It is generally accepted that asymptomatic or incidentally discovered MALS does not warrant intervention.

Laparoscopic release of the arcuate ligament has become a widely accepted treatment. Endovascular therapy may be necessary as well, given the possible recurrence of stenosis. Multidisciplinary assessment by a general surgeon, vascular surgeon, radiologist, and gastroenterologist is helpful.

Cienfuegos et al[6] offered the following selection criteria for laparoscopic treatment: young woman, intense postprandial pain, greater than 70% stenosis of the trunk, and development of collateral circulation.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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EDITORIAL

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Median arcuate ligament syndrome: A clinical dilemma

Compression of the celiac artery was first described in 1917 by Lipshutz,[1] but it took almost 50 years to understand any clinical implication.

The triad of epigastric abdominal pain exacerbated by eating, weight loss, and celiac artery compression was initially described in 1963 by Harjola,[2] leading to the first description of median arcuate ligament syndrome (MALS).

To this day, controversy persists around the pathology of this syndrome, with some groups labeling it a vascular disease, while others consider it a neurogenic disease.

See related article, page 140

Initial treatment was through an open surgical approach, in which the main objective was celiac artery revascularization. The inevitable consequence of this operation was a complete neurolysis performed during exposure of the vessels. This neurolysis is now believed to be the main technical aspect that results in symptom improvement, rather than revascularization. Over the last decade, experience with minimally invasive approaches has grown, and our understanding of the disease has highlighted the role of the celiac plexus nerve fibers as the most relevant anatomic structure related to this syndrome.

A CHALLENGING DIAGNOSIS

Diagnosis remains the most challenging step in treating patients with MALS. Despite growing clinical experience, most published data are limited to case reports and small case-series with limited follow-up. There is no consensus on diagnostic criteria, and surgery does not always result in symptom resolution, with most series reporting between 75% and 85% clinical success.[3]

Recognizing clues

The first suspicion of MALS usually arises when imaging studies reveal stenosis of the celiac artery. Typically, most patients had computed tomography as part of their evaluation for chronic abdominal pain. Cross-sectional imaging can show narrowing of the celiac artery and exclude atherosclerotic disease as a possible etiology.

But a static image is usually not entirely diagnostic. Variation of flow during inspiration and expiration has proven to be one of the most reliable modalities to document true compression with hemodynamic consequences. Peak systolic velocities of more than 249 cm/sec in the expiratory phase with normalization during inspiration are considered pathognomonic for celiac artery compression. But this finding only proves that there is compression of the celiac trunk; it does not imply clinical correlation with symptoms.

Patients with chronic abdominal pain can benefit from a multidisciplinary evaluation

Excluding other foregut conditions

MALS is considered a diagnosis of exclusion, and therefore, testing to exclude other foregut pathology should be considered. This may include endoscopy, abdominal imaging (ultrasonography or computed tomography), and functional gastrointestinal studies. Epigastric pain and weight loss can be a manifestation of other disease processes such as biliary colic, gastroparesis, and peptic ulcer disease that should be excluded.

SURGERY DOES NOT ALWAYS CURE

At my institution, we have strongly advocated for celiac plexus blockade as a diagnostic

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modality and predictor of success. It is a very important tool that can help the patient and clinician make a decision toward proceeding with surgical intervention. Nonresponders tend to have a lower likelihood of clinical success after surgery.[4]

It is very important for physicians to have proper conversations with patients and explain the potential risks of the operation, as well as the anticipated outcome. Technical success does not always correlate with clinical success, and 15% to 25% of patients can have persistent symptoms despite complete release and neurolysis.[4]

Bleeding during surgery from injury to a major vessel is the most feared complication, and it can be very difficult to manage during minimally invasive approaches. It is the most common reason for conversion to open surgery and can ultimately result in major morbidity and, potentially, death.

KEY CONSIDERATIONS IN THE EVALUATION

It is important for clinicians evaluating patients with abdominal pain to understand that an imaging finding of celiac artery compression is not diagnostic of MALS. This syndrome requires careful and meticulous evaluation to rule out more common pathology.

Patients suffering from chronic abdominal pain are often exposed to a long course of nondiagnostic testing and missed diagnosis, which typically results in extreme frustration and a sense of hopelessness. As in many cases of chronic illness, these patients benefit from a multidisciplinary evaluation that typically includes a medical specialist, chronic pain specialist, psychologist, and, ultimately, a surgeon with expertise in the field.

DISCLOSURES

The author reports no relevant financial relationships which, in the context of his contributions, could be perceived as a potential conflict of interest.

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A cutaneous clue to HIV infection

A 66-year-old man presented to the emergency department with 1 month of fevers, nonproductive cough, and progressively worsening dyspnea on exertion despite prior treatment for presumed community-acquired pneumonia.

He was a retired long-haul truck driver who had traveled throughout the United States. He said he had no domestic or occupational exposures to animals or unusual materials. He said he was sexually active with 1 female partner, using condoms. He had no risk factors for human immunodeficiency virus (HIV) infection, including intravenous drug use.

On further review of systems, he reported unintentional weight loss and an isolated facial rash that developed without a known trigger. Physical examination revealed mild tachypnea (22 breaths per minute), oxygen saturation of 89% on room air, clear lungs by chest auscultation, and a markedly erythematous, greasy, scaly rash on his forehead (**Figure 1**) and nasolabial folds.

Possible causes of the rash included atopic dermatitis, tinea, malar rash of systemic lupus erythematosus, and rosacea. However, the location, quality, and appearance of the rash were most consistent with severe seborrheic dermatitis. The combination of seborrheic dermatitis, fevers, respiratory symptoms, hypoxia, and weight loss prompted an HIV test, which returned positive. When we reviewed the HIV test result with the patient, he revised his previous sexual history to include frequent, unprotected sexual intercourse with prostitutes at truck stops while he was a truck driver.

Chest radiography showed diffuse interstitial infiltrates (**Figure 2**). His CD4 count and percentage were low at 313 cells/mL and 27%, and a beta-D-glucan test for fungal infection was markedly elevated at greater than 500 pg/mL (positive ≥ 80 pg/mL), raising a strong

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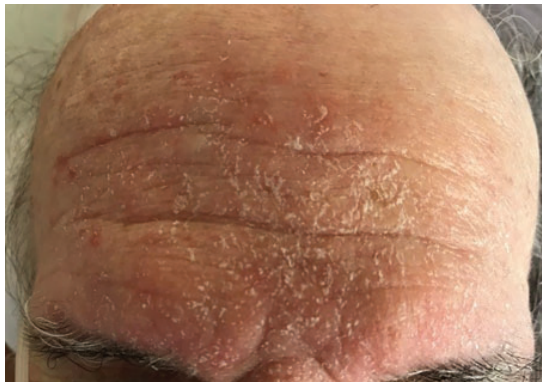

Figure 1. The rash at presentation.

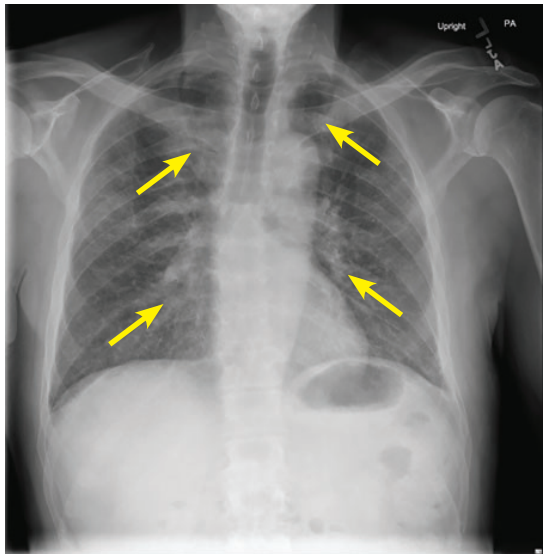

Figure 2. Initial radiography showed diffuse interstitial infiltrates.

A retired trucker presented with fever, cough, dyspnea, and a rash on his forehead

suspicion for *Pneumocystis jirovecii* pneumonia, the most common HIV-associated opportunistic pulmonary infection.

The patient was scheduled for bronchoalveolar lavage, but this procedure was canceled due to a shortage of staffing that prompted cancellation of nonemergency patient procedures.

In light of the patient's history, physical examination, HIV test result, elevated beta-D-glucan, and negative workup including induced sputum for other fungal, viral, and bacterial etiologies, he was treated empirically for *P jirovecii* pneumonia[1,2] with trimethoprim-sulfamethoxazole for 21 days, and was started on combined bictegravir, emtricitabine, and tenofovir alafenamide for HIV.

His condition improved rapidly. On hospital day 5 his oxygen saturation was normal, and he was discharged home to complete his therapy.

His condition improved rapidly with trimethoprim-sulfamethoxazole, and he was discharged 5 days later

SEBORRHEIC DERMATITIS IN HIV INFECTION

Seborrheic dermatitis is a common skin disorder, observed worldwide in infancy and adulthood. HIV infection is a well-established risk factor, with an incidence between 30% and 80% compared with 1% to 3% in the general adult population.[3,4] Seborrheic dermatitis is also associated with other intrinsic risk factors: immunocompromised state after organ transplant; neurologic and psychiatric disorders like Parkinson disease, epilepsy, and depression; and dermatologic disorders like acne, psoriasis, and rosacea.[4]

The severity ranges from mild and self-limiting in infants with "cradle cap," to sometimes severe and persistent in adults with HIV infection and low CD4 counts (200–500 cells/mL).[5]

Treatment is multifaceted with consideration of the patient's age, risk factors, chronicity of symptoms, and compliance with established therapies such as topical antifungals and corticosteroids.[6]

In summary, seborrheic dermatitis can serve as an invaluable bedside clue to HIV infection and can prompt earlier diagnosis in patients who report no risk factors for infection. ■

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DISCLOSURES

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Not all wheezing is COPD

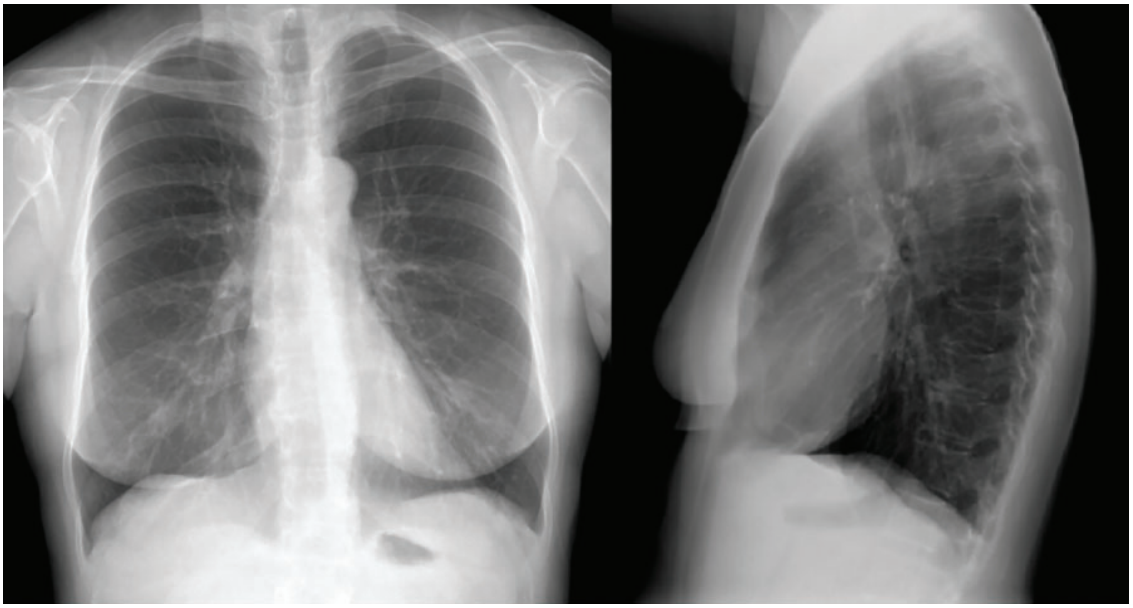

Figure 1. Chest radiography, posteroanterior and lateral views, showed normal findings.

The patient had been hospitalized at least twice in 3 years for 'asthma exacerbations'

A 53-year-old woman came to us because of shortness of breath. The problem had started about 3 years earlier, had slowly gotten worse, and was now limiting her activities of daily living. It was associated with wheezing, and her primary care physician had diagnosed it as asthma. Since that time, she had been hospitalized at least twice with "asthma exacerbations," which were treated with systemic corticosteroids and intravenous antibiotics.

See related editorial, page 150

She had then been referred to a pulmonary physician for spirometry, which showed severe obstruction that did not reverse with bronchodilators. Her condition was diagnosed as chronic obstructive pulmonary disease (COPD) and was treated with montelukast and the combination of inhaled budesonine and formoterol at home.

These drugs did not relieve the symptoms, and she continued to have shortness of breath and wheezing, mainly on exertion. Her BODE index, which is used to predict mortality in COPD, was 5. BODE is an acronym that stands for body mass index, airflow obstruction [forced expiratory volume in 1 second (FEV_1)], dyspnea, and exercise [6-minute walk distance]. The minimum score is 0 and the maximum score is 10. Lower scores are better than higher: a score of 5 indicates more than a 50% chance of death in 4 years.

The patient never smoked or used illicit drugs. She worked as a teacher most of her life and reported no environmental exposure to fumes or dust. She had never undergone endotracheal intubation. She was referred to our clinic for evaluation for a lung transplant.

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TABLE 1

Results of spirometry

	Reference value	Patient's value	Percent of predicted
Forced vital capacity (FVC)	3.60 L	3.22 L	90%
Forced expiratory volume in 1 second (FEV_1)	2.83 L	0.98 L	35%
FEV_1/FVC	80	30	
Forced expiratory flow 25%–75%	2.70 L/sec	0.59 L/sec	22%
Peak expiratory flow	6.03 L/sec	1.22 L/sec	20%
Vital capacity	3.60 L	3.26 L	91%
Residual volume	1.86 L	2.06 L	111%
Total lung capacity	5.15 L	5.32 L	103%

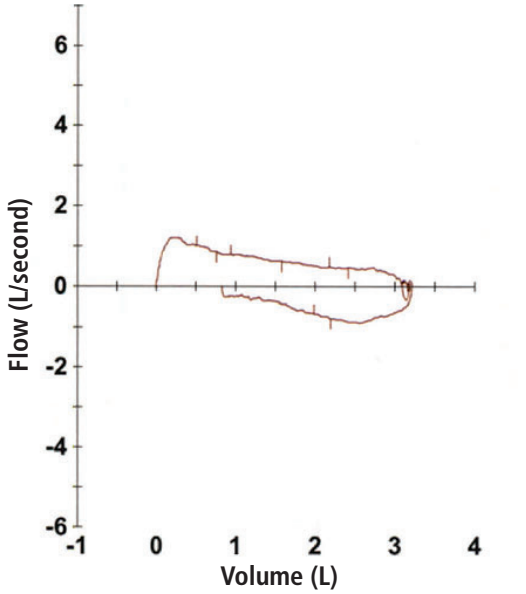

Figure 2. Flow-volume loop showed a decrease in inspiratory and expiratory flow suggestive of fixed extrathoracic airway obstruction.

PHYSICAL EXAMINATION AND WORKUP

Her symptoms completely resolved after treatment

The patient weighed 52 kg and her height was 155 cm. Her blood pressure was 132/84 mm Hg, heart rate 82 beats per minute, and respiratory rate 18 breaths per minute. General inspiratory and expiratory stridor sounds were detected in both lung fields and in the anterior neck area. The rest of the systemic examination was unremarkable.

Chest radiography (**Figure 1**) and computed tomography of the chest were normal.

Spirometry showed severe obstructive pulmonary disease, and her forced vital capacity and FEV_1 did not change when she was given a bronchodilator. Lung volume showed no evidence of air trapping or hyperinflation (**Table 1**). A flow-volume loop showed obstruction during inspiration and exhalation, suggesting a fixed extrathoracic airway obstruction (**Figure 2**).

Flexible fiberoptic bronchoscopy was performed to evaluate the upper airway. The larynx was normal in shape, without laryngomalacia, and the vocal cords had synchronized movement with no abnormalities detected. However, an incomplete ring of tissue (web) was found about 1 cm below the vocal cords (**Figure 3**).

The patient underwent resection of the tracheal web with endobronchial argon plasma coagulation. Afterward, bronchoscopy showed appropriate dilation of the tracheal stenosis (**Figure 4**), and her symptoms significantly improved. She was followed in the pulmonary clinic for 1 year, during which her symptoms completely resolved, and repeat pulmonary function testing showed normal findings.

DISCUSSION

Tracheal web is a tissue layer covering the tracheal lumen. The web is usually incomplete and is not associated with a tracheal cartilage abnormality or deformity.

Congenital tracheal web is a rare anomaly. In children, the incidence has been estimated at 1 in 10,000 births.[1] In adults, a few cases have been found incidentally during planned endotracheal intubation.[1–5] In addition, tracheal stenosis can be a late complication of endotracheal intubation or tracheostomy in adults, and so can tracheal web, although it is rare.[6,7]

Tracheal web is usually misdiagnosed as asthma or COPD.[2,6,8] In our patient, the correct diagnosis was missed by multiple physicians over many years, leading to inappropriate referral for lung transplant.

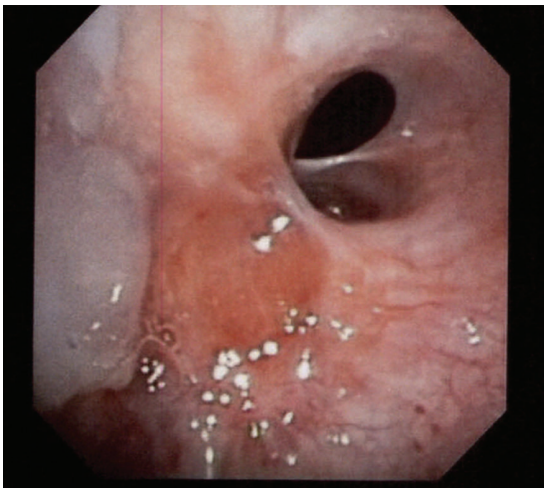

Figure 3. Tracheal web was seen below the vocal cords on flexible bronchoscopy.

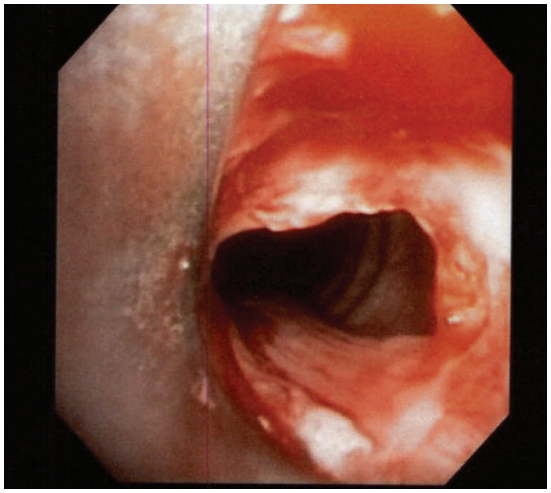

Figure 4. Resection of tracheal web performed with successful endobronchial argon plasma coagulation dilation.

Bronchoscopy combined with computed tomography reconstruction is a reliable and sensitive method of evaluating tracheal web in suspected cases.[6,9] It is also important to examine the flow-volume loop obtained during spirometry. Sometimes a rare diagnosis like tracheal web can be easily identified, and appropriate management can be rendered.

DISCLOSURES

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All that wheezes…

Wheezing is a common symptom often associated with airway obstructive diseases such as asthma and chronic obstructive pulmonary disease (COPD). Dr. Chevalier Jackson, a prominent otolaryngologist of the late 19th and early 20th century, is credited with the aphorism, "All that wheezes is not asthma."[1] However, all that wheezes is obstruction of one kind or another.

See related article, page 147

In this issue of *CCJM*, Patel and Madan[2] describe a patient with shortness of breath and wheezing who was ultimately found to have a tracheal web causing her symptoms. Here, we offer additional comments on this patient's course, including historic features of the case, utility of the physical examination, and the value of pulmonary function testing.

Asthma and COPD are common, but clues may point to another diagnosis

HISTORIC FEATURES OF THE CASE

Patel and Madan's patient was a 53-year-old woman, a nonsmoker, with shortness of breath of 3 years' duration who had been diagnosed first with asthma and then with COPD. She had been hospitalized twice for presumed asthma exacerbations, without response to systemic steroids and antibiotics. Spirometry demonstrated severe obstruction that did not respond to a bronchodilator and normal lung volumes that showed no evidence of hyperinflation or air trapping. After reevaluation by a pulmonologist, the diagnostic key was her spirometric flow-volume loop. Ultimately, she was found to have a tracheal web by bronchoscopy and was successfully treated with endobronchial argon plasma coagulation.

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CLUES TO THE CAUSE OF WHEEZING

In fairness to those who treated her for asthma and COPD, these obstructive diagnoses are common causes of shortness of breath and wheezing, and an empiric trial of therapy is often reasonable. However, we guess there may have been clues early in her course to suggest this was not ordinary obstructive disease. Using this case, we offer a systematic approach to dissecting the etiology of wheezing by reviewing the patient's history, physical examination, and pulmonary function testing.

The patient's history

This patient presented with progressive shortness of breath, although it is unclear whether it was variable, which is usually a feature of asthma, especially early on. We know she had never smoked. Nonsmokers can, of course, have asthma, and they can also have COPD, but this is much less common.

Whenever a nonsmoker is diagnosed with COPD, it is worth asking about possible exposure to biomass fuels (rare in developed areas of the world), other airway irritants, and underlying predisposing conditions. Anyone suspected of having COPD, regardless of smoking history, should also be tested for alpha-1 antitrypsin deficiency, with both alpha-1 antitrypsin level and genotype analysis.

COPD severity is often classified according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (**Table 1**), which determines its suggested treatment.[3] Our patient would be classified as being in group D based on frequent hospitalizations and severe symptoms, which would generally require therapy with long-acting bronchodilators and possibly inhaled corticosteroids.[3]

TABLE 1

Global Initiative for Chronic Obstructive Lung Disease classification of COPD, with recommended therapy

Exacerbations	mMRC 0–1; CAT < 10	mMRC ≥ 2; CAT ≥ 10
0 or 1 moderate exacerbation in the past year (not leading to hospital admission)	**Group A** Short- or long-acting bronchodilator	**Group B** LABA or LAMA
≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization within the past year	**Group C** LAMA	**Group D** LAMA or LAMA + LABA or inhaled corticosteroid + LABA

CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; LABA = long-acting beta-2 agonist; LAMA = long-acting muscarinic receptor antagonist; mMRC = Modified Medical Research Council dyspnea questionnaire

Adapted from Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2019. Accessed February 10, 2021. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf

These treatments were ineffective. Once it became clear that usual therapies for both asthma and COPD were ineffective, an in-depth evaluation of her airway disease was indicated.

The physical examination

Our patient apparently had wheezing early on, although we are not told whether she herself heard any airway noise or whether it was appreciated only on examination. Wheezing is typically a sign, not a symptom, meaning the sound is detected on lung auscultation, and usually the patient is unaware of it. If the patient reported her own wheezing, then we should immediately suspect the airway noise is probably stridor.

Careful examination can usually distinguish these 2 different airway sounds. Wheezing is the polyphonic (multipitch or "musical") sound made by airflow through small and medium airways, the "distal" airways. It is predominantly or often exclusively heard on expiration due to lung parenchyma compression during expiration, which further narrows the distal airways. No distinguishing feature of wheezing can tell us whether it is due to asthma or COPD. Either diagnosis may be associated with rhonchi or other additional airway sounds.

Stridor is the sound made by airflow through an obstructed large central (proximal) airway. Some causes of stridor cause obstruction exclusively on expiration or inspiration, but many cause obstruction during both phases of breathing. Also, since stridor is usually caused by a focal narrowing at one point in the airway, its pitch is usually constant or monophonic.

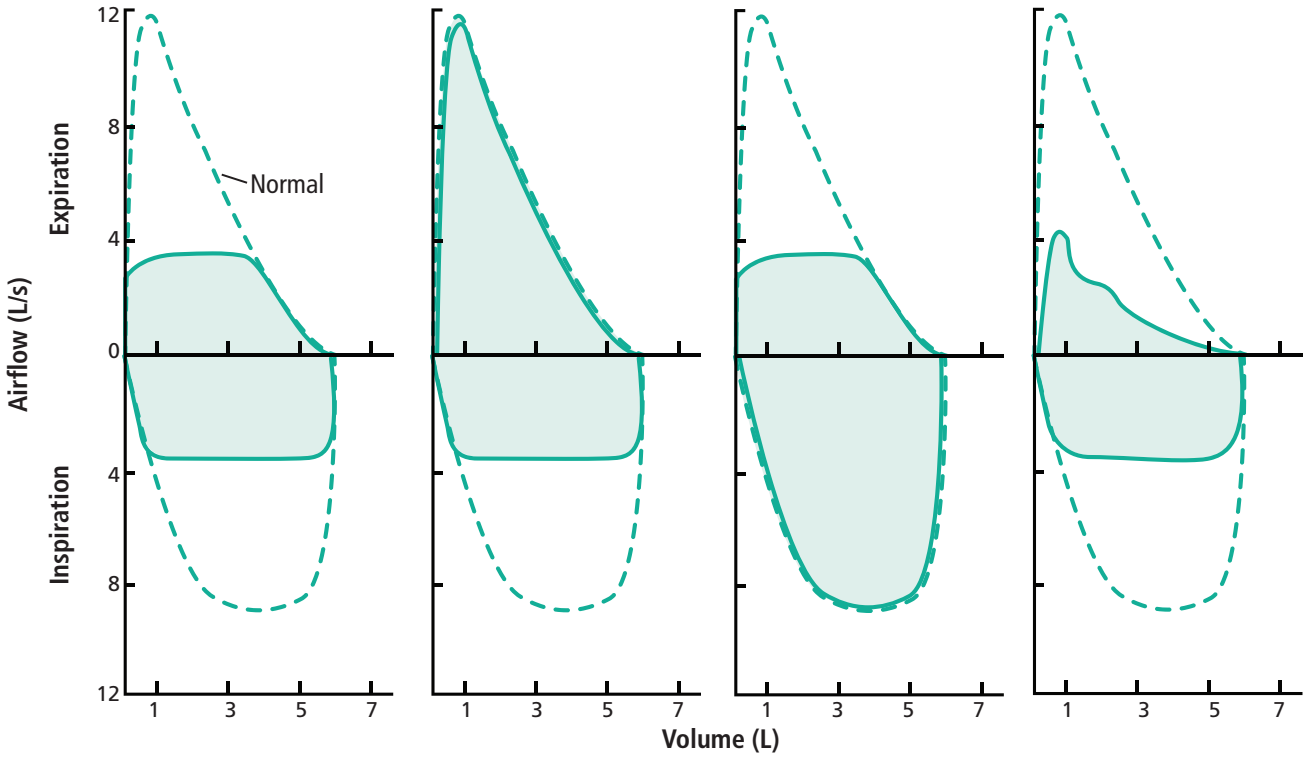
It is likely that this woman's airway noise was monophonic and heard during both inspiration and expiration, both features suggestive of stridor.

The hallmark of obstruction is a reduced FEV_1/FVC ratio

Pulmonary function testing

The hallmark of obstruction on pulmonary function testing is a reduced ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC), meaning that the FEV_1 is reduced out of proportion to the FVC.[4] Since a reduced FEV_1/FVC ratio reflects decreased airflow, this pattern is seen in any condition that inhibits or "obstructs" that flow, such as asthma, COPD, or a fixed narrowing of an airway.

Fortunately, pulmonary function testing gives additional information that can help identify more specific causes of reduced flow. As a general rule for variable obstruction lesions, an upper airway obstruction (outside



A Fixed upper airway obstruction

Vocal cord paralysis

Laryngeal or tracheal web

Tracheal stenosis

Retropharyngeal abscess

B Variable extrathoracic obstruction

Infectious laryngotracheobronchitis

Thyromegaly

Tracheomalacia

Anaphylaxis

Foreign body aspiration

C Variable intrathoracic obstruction

Tracheal stenosis

Foreign body aspiration

Endobronchial tumor

D Lower airway obstruction

Asthma

COPD

Pulmonary edema

Aspiration

Pulmonary embolism

Bronchiolitis

Cystic fibrosis

Bronchiectasis

Based on information from reference 4.

Figure 1. Attenuation of the flow-volume loop in different types of airway obstruction.

the thorax) will predominantly limit inspiratory flow (**Figure 1B**), whereas intrathoracic obstruction will mostly decrease the expiratory flow (**Figure 1C**). Our patient's flow-volume loop showed attenuation of both expiratory and inspiratory flow, suggestive of a central fixed obstruction (**Figure 1A**).

Pulmonary function testing cannot diagnose a tracheal web. Only bronchoscopy can show the specific cause of obstruction, but the flow-volume loop is the strongest evidence before invasive inspection that the problem is not a distal airways disease like asthma or COPD.[6]

TAKE-HOME MESSAGE

It is always far easier to critique the diagnostic missteps of others than to make the correct diagnosis yourself. We make no claims of always going straight to the right answer in our own clinic. The case reported by Patel and Madan is an excellent example of the diagnostic pitfalls presented by common combinations of complaints and findings. A thorough and systematic approach, emphasizing the medical history, the physical examination, and the correct interpretation of pulmonary function test results ultimately led the clinicians to the correct diagnosis.

Perhaps the take-home message is that while we enjoy unprecedented diagnostic advantages due to advanced and emerging technology, in the end, even rare and unusual diseases are usually identified with the fundamental tools of a sound history, physical examination, and basic, targeted testing.

DISCLOSURES

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Anterior interosseous nerve palsy caused by Parsonage-Turner syndrome

A 58-year-old man presented with difficulty in moving his left hand. Three weeks before this presentation, he had symptoms of an upper respiratory tract infection, which resolved spontaneously in several days. And 1 week after that, he experienced a severe stabbing pain in his entire left upper arm, which resolved in several days. At that time, he also developed difficulty in moving the thumb and index finger of his left hand.

On physical examination, manual muscle testing showed weakness in the left opponens pollicis muscle and flexor digitorum profundus muscle of the left index finger, without apparent atrophy. There was no evidence of sensory disturbance. Tendon reflexes were normal in the upper and lower extremities, and pathological reflexes were negative.

The OK sign test was positive in the left hand (**Figure 1**). Blood tests, cervical magnetic resonance imaging, electromyography, and nerve conduction velocity testing showed no abnormal findings. Based on the history, symptoms, OK sign test, and lack of abnormalities on other parts of the workup, the patient was diagnosed with Parsonage-Turner syndrome.

His symptoms resolved in several months after rehabilitation with physical therapy.

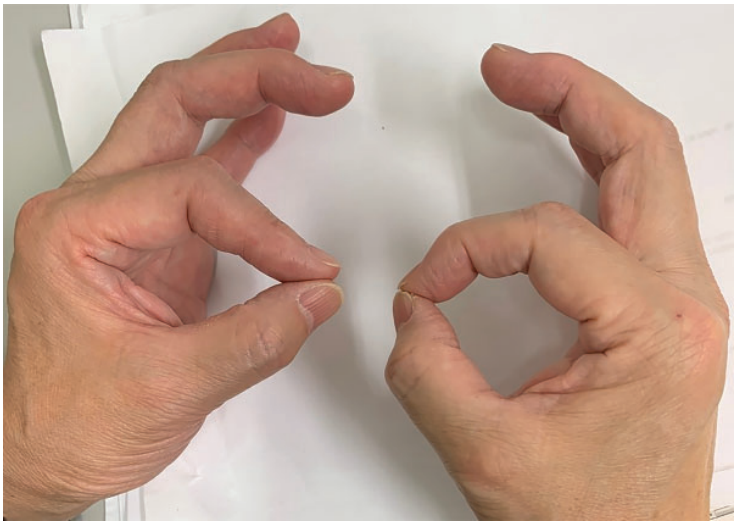

Figure 1. The OK sign test was positive in the left hand, with reduced flexion in the first interphalangeal joint and the second distal interphalangeal joint, as compared with the corresponding joints of the nonaffected (right) hand.

PARSONAGE-TURNER SYNDROME: DISTINGUISHING FEATURES

Parsonage-Turner syndrome, also referred to as idiopathic brachial plexopathy or neuralgic amyotrophy, is characterized by an acute onset of unilateral neuralgia of the upper extremity.[1] The neuralgia resolves in several days to 2 weeks.[1] Thereafter, muscle atrophy and motor paralysis develop in the ipsilateral side.[1] The most commonly affected muscles are proximal ones, including the supraspinatus, infraspinatus, anterior serratus, deltoid, and biceps brachii.[2] Cases of selective anterior-posterior interosseous nerve palsy have also been reported.[3]

The anterior interosseus nerve is a branch of the median nerve, which supplies motor innervation to the anterior forearm flexors, the thenar muscles, and the lateral 2 lumbricals. It also supplies sensory innervation to the lateral palm and anterior lateral 3 and one-half fin-

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gers. Both proximal median nerve palsy above the elbow and carpal tunnel syndrome result in reduced sensation in the thumb, index finger, and middle finger. Anterior interosseus nerve palsy alone does not cause sensory disturbance.

Akane et al[4] reported that 27 of 51 (52.9%) patients with anterior-posterior interosseous nerve palsy had preceding upper extremity pain, and 9 of the 27 (33.3%) had pain in the entire arm. In the cases that began with pain, the first signs of weakness appeared within 7 days in 66.6%. A preceding infection was observed in 3 cases.

The OK sign test is administered by asking patients to make an OK sign with the thumb and index finger. It is positive if it detects reduced flexion in the first interphalangeal joint and the second distal interphalangeal joint, as compared with the corresponding joints of the nonaffected hand, and thus is useful in the diagnosis of anterior interosseous nerve palsy.[5]

Electromyography usually indicates acute denervation and axonal degeneration with potential positive fibrillation spike waves.[6] However, 3.7% of patients with Parsonage-Turner syndrome show no abnormalities on electromyography[2] because the alterations are generally not perceptible until 3 weeks after the onset of symptoms.[6] Some cases also reported no abnormalities on magnetic resonance imaging or nerve conduction velocity testing.[4] As patients with interosseous nerve palsy often lack characteristic imaging findings, careful history-taking is important in the diagnosis.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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REVIEW

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Vaccination in pregnancy: A call to all providers for help

ABSTRACT

Vaccination in pregnancy is an important part of maternity care, but maternal immunization rates continue to be below national benchmarks. Influenza and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccinations have been shown to be safe and provide important protections to pregnant women, the fetus, and neonates. Although obstetrician-gynecologists provide the bulk of pregnancy care, general internists and medical specialists have frequent clinical encounters with maternity patients and should assist in immunization education and administration.

KEY POINTS

Seasonal influenza and Tdap vaccinations are recommended for women who are pregnant or planning pregnancy.

Both vaccines are safe for most women and offer significant benefits to the mother and baby.

Pregnant women should be given the inactivated form of the influenza vaccine, not the live vaccine.

Tdap vaccination is recommended in the third trimester but can be given at any time in pregnancy.

A recommendation from a healthcare provider is the number-one factor consistently shown to increase maternal vaccination rates.

The COVID-19 vaccine should not be withheld from pregnant patients who meet the criteria for vaccination, but the decision is at the discretion of the patient after an informed discussion.

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Vaccination in pregnancy is a public health priority that is often neglected, even more so today with the current focus on COVID-19 vaccination. Vaccination in pregnancy is important to protect the mother (who is especially vulnerable due to the physiologic changes of pregnancy), fetus (because of developmental and prematurity risks), and neonate (by conferring passive immunity).

This article reviews the 2 vaccines most often given in pregnancy: the inactivated seasonal influenza vaccine and the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine, along with evidence of their benefits and safety, guidance on administering them, and management of pregnant women who become sick with or are exposed to influenza or pertussis.

VACCINATION IS RECOMMENDED IN PREGNANCY

The American College of Obstetricians and Gynecologists (ACOG) advises that not only obstetrician-gynecologists but other healthcare providers recommend and give the influenza vaccine to women who are pregnant or plan to become pregnant during the influenza season.[1] They also recommend that women be vaccinated against tetanus, diphtheria, and pertussis during every pregnancy.[2]

Despite recommendations from national and international societies, vaccination rates in pregnancy remain lower than targets.[3] Internists and medical specialists play a critical role in increasing vaccination rates in pregnant women. Because these providers provide ongoing care and surveillance of medical comorbidities such as asthma, diabetes, lupus, and cardiac disease during pregnancy, their action to recommend

TABLE 1

Summary of vaccinations in pregnancy

Vaccine	Indicated during every pregnancy	Indicated for specific populations in pregnancy	Contraindicated in pregnancy	Postpartum and nursing
Seasonal influenza	√			√
Tdap	√			√
Pneumococcal		√		√
Hepatitis A		√		√
Hepatitis B		√		√
MMR			√	
Varicella			√	

MMR = measles, mumps, rubella; Tdap = tetanus toxoid, reduced diphtheria, and acellular pertussis

and administer immunizations to women who are pregnant or planning a pregnancy is needed to increase vaccination rates.

Table 1 summarizes maternal immunization recommendations.

Vaccination rates in pregnancy remain lower than targets

INFLUENZA VACCINATION

Although influenza vaccination rates increased after the 2009 H1N1 pandemic up to a high of just over 50% in 2016 in the United States,[4] rates in pregnancy are declining.

Immunization of pregnant women against seasonal influenza is critically important. During the 2009 H1N1 influenza pandemic in the United States, 5% of all influenza deaths were in pregnant women, although pregnant women make up only 1% of the population.[4]

Influenza in pregnancy places the mother at higher risk of pneumonia, hospitalization, respiratory failure, and intensive care unit admission compared with nonpregnant women. These risks are due to immunologic changes in pregnancy such as altered T-cell immunity and physiologic changes such as the gravid uterus crowding into the chest, causing decreased functional residual capacity of the lungs. Influenza can also lead to preterm labor and birth, potentially subjecting the fetus to the effects of prematurity or causing stillbirth.[5]

Benefits of influenza vaccination for mother and baby

Vaccination in pregnancy is beneficial for both mother and baby. The effectiveness of seasonal influenza vaccination is similar between pregnant and nonpregnant women.[6] Although the efficacy of the seasonal vaccine varies from year to year, pregnant women who have been vaccinated have fewer hospital admissions than those not vaccinated.[1,4]

Vaccinating the mother can also have substantial benefits for the newborn after birth, owing to passive immunity conferred by transplacental passage of maternal antibodies. A randomized study found umbilical cord blood antibody titers to be more than 1.5 times higher than those in maternal blood after vaccination.[7] Clinical benefits include fewer hospitalizations and lower rates of laboratory-confirmed influenza illness in infants born to vaccinated mothers. In 2 studies, 93 of 2,873 (3.24%) infants of vaccinated women developed laboratory-confirmed influenza illness compared with 142 of 2,869 (4.95%) infants of unvaccinated women (risk ratio 0.66, 95% confidence interval 0.50–0.85).[8] From these data we calculate the absolute risk reduction as 1.71% and the number needed to treat 58.

No evidence of safety concerns

Numerous studies have found influenza vaccination to be safe and effective in pregnancy, with few adverse effects on the mother.[1,4,5] Common vaccine-related side effects include injection site reaction, fever, headache, and myalgia.

Possible adverse effects of the seasonal flu vaccine on the fetus and neonate have also been studied. Systematic reviews of maternal inactivated influenza virus vaccination have found no correlation with increased fetal risk.[9,10] A prospective cohort study of more than 10,000 pregnant women found no association between influenza vaccination in pregnancy and adverse birth outcomes.[11] Although concerns have been raised about the safety of the mercury-containing preservative thimerosal and its possible links to autism, no scientific evidence of a link between receipt of thimerosal-containing vaccines in the mother and adverse health or developmental effects in the baby has ever been found.[1]

Administration recommendations

Only the inactivated influenza vaccine should be used for pregnant women. The live, attenuated influenza vaccine is indicated for nonpregnant patients ages 2 to 49, and it may be used for postpartum women, including those who are breastfeeding.

Contraindications. A prior life-threatening reaction to the influenza vaccine or to any of its components is an absolute contraindication to receiving the vaccine. Even for women with a history of egg allergy or Guillain-Barré syndrome, vaccination should be considered if the potential benefits outweigh the risks.[12]

Timing. Pregnant women can receive the inactivated influenza vaccine at any time during influenza season (typically October through May), although the best time is early in the season, ideally before the end of October. An unvaccinated pregnant woman presenting to her primary care provider or medical specialist should be encouraged to receive the vaccine regardless of her stage of pregnancy.

Women of reproductive age who are planning a pregnancy during flu season or are not actively using contraception should be given the vaccine.

Documentation of vaccination should be provided to the patient to ensure her immunization records are kept current.

Family members of pregnant women should also be vaccinated. Although this strategy is recommended to reduce illness in newborns, data are mixed about its efficacy.[5]

Treating influenza and possible exposure

Whether or not they have been vaccinated, women who develop flulike illness at any time during pregnancy should be prescribed antiviral medications, ie, one of the following regimens, depending on local influenza virus resistance[13]:

- Oseltamivir 75 mg twice daily for 5 days (recommended by the US Centers for Disease Control and Prevention)
- Zanamivir 10 mg (2 5-mg inhalations) twice daily for 5 days
- Peramivir 600 mg (single intravenous infusion).

Treatment should be initiated as soon as possible after onset of illness.

Postexposure antiviral prophylaxis should be considered for pregnant and postpartum women, with either of the following regimens:

- Oseltamivir 75 mg once daily for 7 to 10 days
- Zanamivir 10 mg (2 5-mg inhalations) once daily for 10 days).

Therapy should be given presumptively without laboratory confirmation if suspicion is high for pregnant women and women who are up to 2 weeks postpartum, including women who have experienced a fetal loss.

Only the inactivated influenza vaccine should be used for pregnant women

TDAP VACCINATION

Tdap vaccination is recommended during pregnancy by the Advisory Council on Immunization Practices (ACIP) and ACOG, primarily to help protect neonates against the highly contagious *Bordetella pertussis* bacteria.[14] Despite that, the rate of Tdap immunization in pregnancy hovers just over 50%.

Infants younger than 1 year are at the highest risk of severe symptoms and sequelae from pertussis; it is a major cause of vaccine-preventable death in this age group.[15]

Vaccination is highly effective in protecting infants against pertussis infection, preventing over 90% of hospitalizations and 95%

of deaths due to pertussis in the first 2 to 3 months of life.[16] Vaccination during pregnancy is especially important, as it bolsters maternal pertussis-specific IgG antibodies, which are passively acquired by the fetus during pregnancy.[17] Without maternal vaccination, there is a gap in protection after delivery, as infants are unable to receive their first pertussis vaccination until 6 weeks of age, when they start their 5-dose course at set intervals between 2 months and 6 years of age.[14]

Timing of Tdap immunization

Tdap should be given to pregnant women at the beginning of the third trimester of each pregnancy, ideally between 27 and 36 weeks gestation, regardless of timing of prior Tdap vaccination. It can be given earlier in pregnancy for maternal benefit (such as tetanus exposure), and in such cases, does not need to be repeated later in pregnancy or postpartum. For women who did not receive Tdap prenatally, it can be given postpartum. It should not be given preconception unless the patient is due for her scheduled vaccination.

Pertussis vaccination is contraindicated for patients who have had a severe allergic reaction after a previous dose or encephalopathy without identifiable cause within 7 days of receiving a pertussis vaccine.

Pregnant women who develop flulike illness should be prescribed antiviral medications

Vaccinating family members

Since 2005, the ACIP has recommended a strategy of "cocooning" (ie, vaccinating people who come into close contact with a newborn) to provide the best protection against pertussis until the recommended childhood vaccination schedule can begin.[14] However, programs using this strategy have had inconsistent results due to challenges in vaccinating other family members. Also, evidence suggests that immunization with Tdap may not fully prevent bacterial transmission. Nevertheless, the ACIP continues to recommend this practice, and primary care physicians, who may care for multiple members of a family, may be able to promote this policy.

Addressing safety concerns

The maternal and fetal safety of Tdap vaccination has been well documented,[18] and it does not increase pregnancy risks such as preeclampsia, fetal growth restriction, stillbirth, or preterm birth.[19] No fetal or neonatal developmental risks have been identified. Similar to the seasonal influenza vaccine, common reactions to maternal Tdap administration include pain at the injection site, headache, and fatigue.

Treating pertussis exposure

Although pertussis is primarily managed through vaccination in the United States, infection does occur. Pertussis has 3 stages: a catarrhal stage with upper respiratory infection symptoms, a paroxysmal stage with coughing spasms, and a convalescent stage with slow resolution of coughing frequency and severity. Patients are most infectious during the catarrhal and paroxysmal stages.[20]

If a pregnant patient or a household contact has been exposed to pertussis, treatment should begin within 21 days of exposure to reduce symptomatic infection and spread. Treatment for pregnant adults is with one of the following regimens[21]:

- Azithromycin 500 mg in a single dose on day 1, then 250 mg per day on days 2 through 5
- Erythromycin 2 g per day in 4 divided doses for 14 days.

Treatment of the mother is especially important during the postpartum period to reduce the risk of spread to the newborn. Either regimen is safe during lactation.

ALL PHYSICIANS SHOULD PROMOTE VACCINATION

Primary care providers and medical specialists should routinely assess the vaccination status of their patients, especially pregnant women, and recommend and administer appropriate vaccines. Although obstetrician-gynecologists bear primary responsibility for providing and administering vaccinations to pregnant patients, not all carry influenza or Tdap vaccines in their offices due to financial or logistical reasons, such as storage or tracking of vaccines.[22] A national US survey of obstetrician-gynecologists found that for those whose practice did not stock an indicated vaccine, 56% "always or often" referred patients to their primary care provider to receive the vaccine, referring less often to public health departments (32%) or pharmacies (25%).[22]

Many pregnant women refuse the Tdap and influenza vaccines[23] for a variety of reasons,[24] including common misperceptions ("It will make me sick"), concerns for the safety of the fetus or neonate, and personal health beliefs ("I never get the flu shot"). A review by Mossad[25] provides guidance on counseling patients who doubt the value of immunization.

Studies of various vaccine promotion techniques, such as text messaging or video tutorials, have found that they result in only modest, if any, increase in maternal vaccination acceptance.[26,27] Multiple studies have shown that the recommendation of a healthcare provider is the single most influential factor of pregnant women accepting vaccinations in pregnancy.[4,23,28]

COVID-19 VACCINATION IN PREGNANCY

In December 2020, the US Food and Drug Administration issued an Emergency Use Authorization for 2 of the vaccines against SARS-CoV-2 (COVID-19).

Soon after, ACOG[29] issued a statement about COVID-19 vaccination in pregnancy, stating, "ACOG recommends that COVID-19 vaccines should not be withheld from pregnant individuals who meet criteria for vaccination based on ACIP-recommended priority groups." The US Centers for Disease Control and Prevention (CDC) issued a similar statement.[30] It is recommended, but not required, that pregnant and lactating patients have a discussion with their provider about their own specific circumstances and risks and whether to accept the vaccine.

While no pregnant patients were included in critical vaccine safety trials, it is known that a pregnant woman who contracts COVID-19 is at higher risk of complications compared with her nonpregnant counterparts,[31] and the CDC has responded by including pregnancy as a risk factor for a high-risk health group. As such, pregnant patients, especially those in high-risk occupations, should be offered the vaccine after appropriate counseling as set forth by guidance from ACOG and the CDC.

However, the decision to be vaccinated is solely at the patient's discretion, and a conversation with her healthcare team about her decision to be vaccinated is recommended but not required. Finally, clinicians are encouraged to keep abreast of available evidence about the COVID-19 vaccines in terms of risks and benefits, as well about potential complications, so that they can provide the most accurate information and counseling to their patients. ■

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REVIEW

CME MOC

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Imaging to evaluate suspected infective endocarditis

ABSTRACT

Although echocardiography is fundamental in diagnosing infective endocarditis, sometimes it reveals no evidence of endocarditis while clinical indicators remain consistent with the diagnosis. In such cases, repeat imaging is necessary, and the appropriate timeline for it and whether it should be done with transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), or an advanced imaging method are important.

KEY POINTS

Guidelines recommend TTE as the first test for suspected infective endocarditis, usually combined with TEE.

If imaging findings are negative in a patient in whom the disease is strongly suspected, imaging should be repeated 3 to 7 days later.

TEE is more sensitive than TTE (which is quicker and noninvasive) for diagnosing and characterizing infective endocarditis, but even using TEE, results may be falsely negative before vegetations or other findings of endocarditis are detectable.

Multidetector cardiac computed tomography may be used to better visualize prosthetic valve vegetations, abscesses, pseudoaneurysms, and dehiscence.

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography may be indicated for patients with prosthetic valves or cardiac implantable electronic devices.

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A 68-YEAR-OLD WOMAN with a prosthetic aortic valve presents with fever and acute right lower limb pain. Blood cultures grew Staphylococcus aureus. *Transthoracic echocardiography (TTE) demonstrates satisfactory valve function with no obvious vegetations. Due to ongoing concern about infective endocarditis, transesophageal echocardiography (TEE) is performed. Again, no obvious prosthetic aortic valve vegetations are found.*

Infective endocarditis can be a challenge to diagnose. Echocardiography is the cornerstone of evaluation, but what should be done if no echocardiographic evidence of infective endocarditis is found in a patient who continues to have bacteremia? Key questions in such a situation include:

- When should echocardiography be repeated?
- Should it be TTE or TEE, or should a more advanced imaging method be used?

This article reviews the use of echocardiography for diagnosing infective endocarditis, the emerging roles of advanced imaging methods, current guidelines and their limitations, and special considerations for patients at high risk.

AN OLD PROBLEM IN A NEW DEMOGRAPHIC

Despite advances in imaging and diagnosis, infective endocarditis, an infection of the endocardium or heart valves, remains a serious disease with high morbidity and mortality rates.[1,2] It is most often precipitated by bacteremia; bacteria (most commonly *S aureus* or viridans streptococci) enter the bloodstream and adhere to damaged or abnormal endothelium, resulting in colonization and prolifera-

TABLE 1

Imaging for endocarditis: ESC[10] and AHA[4] recommendations[a]

Obtain echocardiography as soon as endocarditis is suspected (ESC and AHA)

For initial investigation:
Transthoracic echocardiography (TTE) should be used (ESC)
Both TTE and transesophageal echocardiography (TEE) should be used (AHA)

Perform TEE:

If TTE is not diagnostic in patients with known or suspected infective endocarditis (ESC and AHA)

If complications are suspected (eg, new murmur, embolism, persisting fever, heart failure, abscess, atrioventricular block) (ESC and AHA)

If intracardiac device, leads, or prosthetic valves are present (ESC and AHA)

Repeat TEE if initial TTE is negative but clinical suspicion of infective endocarditis remains high:
7–10 days later (ESC), or
3–5 days later (AHA)

[a]All recommendations listed are class 1 (strong).
AHA = American Heart Association; ESC = European Society of Cardiology

Echocardiography is the cornerstone of evaluation

tion with monocyte recruitment, thrombosis, and inflammation.[3]

Infective endocarditis has undergone a demographic shift in recent decades. Formerly it was most often seen in patients with rheumatic or congenital heart disease, but now it is likelier to be associated with hemodialysis, immunosuppression, prosthetic valves, other cardiac devices, or intravenous drug use.[4]

ECHOCARDIOGRAPHY IS ESSENTIAL

Infective endocarditis is diagnosed by the modified Duke criteria, with major and minor criteria used to determine whether it is definitely or probably present.[3] Major criteria include positive blood cultures of typical microorganisms consistent with the disease and echocardiographic evidence.[5] Echocardiography is the key imaging method for diagnosing infective endocarditis and assessing its prognosis.[6]

The major echocardiographic criteria for diagnosing infective endocarditis are vegetations (ie, oscillating or nonoscillating intracardiac masses on a valve, other endocardial structure, or implanted intracardiac material), an abscess, and new dehiscence of a prosthetic valve. Valve destruction, aneurysm, or perforation suggest the diagnosis.[7]

TTE is typically performed initially. It is rapid, noninvasive, widely available, and highly specific, justifying its use as a first-line screening tool.[6,8] However, suboptimal findings are especially likely in patients with prosthetic valves because of poor resolution of prosthetic leaflets due to acoustic shadowing.[9] TEE is used when TTE imaging is suboptimal, or when clinical suspicion remains high in a patient with persistent bacteremia despite negative findings on TTE.

Infective endocarditis is a dynamic process, and infective valvulitis may be present before a discrete vegetation is visible using TTE or TEE.[2] Patients without echocardiographic findings but who still are suspected clinically of having infective endocarditis may either be in the early stages of the disease or have a different disease process.

USE BOTH TTE AND TEE FOR MANY PATIENTS

Guidelines from the European Society of Cardiology (ESC),[10] American Heart Association (AHA),[4,11] and American College of Cardiology (ACC)[11] are summarized in **Table 1**.

ESC guidelines

The ESC guidelines[10] say to perform TTE as soon as infective endocarditis is suspected.[10] TEE should also be performed in many cases because of its superior image quality, spatial resolution, and sensitivity.[7] This applies to a variety of clinical scenarios, including when:

- TTE is negative, but a high clinical suspicion of infective endocarditis remains
- TTE findings are of poor quality
- TTE demonstrates abnormal changes, but the valvular structure needs to be further delineated and involvement of other valvular structures needs to be ruled out
- The patient has a prosthetic valve or intracardiac device.

The only scenario in which TEE is not usually performed after TTE yields negative results is in patients who have bacteremia but a low clinical suspicion of infective endocar-

ditis.[10] This includes those with bacteremia as a result of line-related infections whose symptoms resolve after the line is removed, and those without high-risk features (eg, a permanent intracardiac device, dialysis dependency, or bacteremia for at least 4 days).[12,13]

AHA and ACC guidelines

Recommendations from the AHA[4] and AHA/ACC[11] are similar to those of the ESC.[10] In patients suspected of having infective endocarditis on the basis of the modified Duke criteria (including 2 positive blood cultures), TTE is recommended to characterize anatomic features.[11] TEE is recommended if TTE is not diagnostic, intracardiac leads are present, or complications are suspected. TTE should be performed in all cases of suspected native valve infective endocarditis, with follow-up TEE in 3 to 5 days if clinical findings change or suspicion remains high despite negative findings on TTE. Intraoperative TEE is recommended for patients undergoing surgery.

Adjuvant imaging with multidetector computed tomography (MDCT) can be considered in patients who have unremarkable findings on TTE and TEE if prosthetic or paravalvular infections continue to be suspected.[11]

WHEN SHOULD TTE OR TEE BE REPEATED IF NEGATIVE, BUT BACTEREMIA PERSISTS?

There is some controversy as to when to repeat echocardiography in cases in which both TTE and TEE are unremarkable but the clinical suspicion of infective endocarditis is high. Evidence gaps exist for optimal timing of repeat echocardiography according to patient pathology, risk status, and outcomes.

In these situations, a repeat TEE should be scheduled (ESC guidelines: 7–10 days after an initial negative TEE; AHA guidlines: 3–5 days after an initial TEE). But it is especially important that this should be done only if there is ongoing clinical suspicion for infective endocarditis.

Some studies suggest repeating echocardiography 7 to 10 days later, while others recommend 5 to 7 days (or even earlier in *S aureus* infection).[7,14] Thus, the ESC guidelines recommend repeating TTE or TEE, or both, 7 to 10 days later in cases of an initially negative examination if clinical suspicion of infective endocarditis remains high.[10]

Sochowski and Chan[8] studied 105 patients who underwent TEE for suspected infective endocarditis, of whom 65 had a negative study. In 56 of these 65 patients, an alternative diagnosis was made, in another 5, infective endocarditis was diagnosed by repeat TEE, and the other 4 patients were treated for infective endocarditis without a definitive diagnosis. Gram-positive bacteremia and prosthetic valves were more common in the group with proven infective endocarditis than in those with suspected infective endocarditis but negative findings on TEE, although the difference was not statistically significant ($P = .07$), possibly due to the small sample size. The study reported that the optimal timing for repeat imaging varied by patient.

Other indications for repeating echocardiography include the new onset of complications of infective endocarditis (eg, a new murmur, embolism, heart failure, abscess, atrioventricular block), persisting fever, and follow-up of suspected, uncomplicated infective endocarditis.[4]

TTE or TEE for follow-up?

Evidence is lacking on whether TTE or TEE is more appropriate when echocardiography should be repeated.[10] TEE remains superior in assessing for evidence of infective endocarditis. Studies from the 1980s and 1990s found TEE to be more sensitive than TTE in detecting valvular vegetations: 100% vs 63% (N = 96),[15] 94% vs 44% (N = 66),[16] and 87% vs 69% (N = 64).[17] Daniel et al[18] also found TEE to be more sensitive than TTE for detecting valvular abscesses: 87% vs 28% (n = 118). However, these studies were small and were done decades ago, and echocardiography has undergone many advances since then, including 3-dimensional TEE.

Infective endocarditis has undergone a demographic shift

NATIVE VS PROSTHETIC VALVE

TEE is more sensitive than TTE for diagnosing infective endocarditis regardless of whether a native or prosthetic valve is involved. However, some differences should be kept in mind.

Use TEE for native valve evaluation

In native valve endocarditis, the diagnostic accuracy of TTE depends on the size of veg-

etations and underlying valvular disease, with sensitivity ranging from 40% to 63% compared with 90% to 100% for TEE.[19]

Reynolds et al[20] evaluated TTE incorporating harmonic imaging for 51 vegetations seen on TEE. The sensitivity of TTE in detecting native valve vegetations was only 55%, and the size of the vegetation affected the sensitivity. When TTE was positive, vegetation size on TEE was significantly larger than when TTE was falsely negative, which was true for aortic valves (11.2 ± 3.4 mm vs 5.8 ± 3.6 mm, $P = .001$) and for mitral valves (12.9 ± 4.1 mm vs 7.9 mm ± 5.0 mm, $P = .01$). Furthermore, TEE was able to reveal additional diagnoses not seen by TTE in 7 patients (14%), including aortic valve prolapse, aneurysm, and vegetations on intervalvular fibrosa and pacemaker wires.

Use TEE and consider advanced imaging for prosthetic valves

In prosthetic valve endocarditis, vegetations are more difficult to detect, and TEE is typically used in conjunction with TTE for diagnosis.[19]

Use of MDCT

Major echocardiographic diagnostic criteria are vegetations, abscess, and new dehiscence of a prosthetic valve

In a systematic review and meta-analysis of 20 studies in 496 patients, Habets et al[21] found the pooled sensitivities for detecting prosthetic valve vegetations were 82% using TEE, 88% using TEE plus MDCT, and 29% using TTE alone. The pooled sensitivities for detecting life-threatening periannular complications (eg, abscesses and mycotic aneurysms) were 86% using TEE, 100% using TEE and MDCT, and 36% using TTE alone.

Use of FDG-PET/CT

The added diagnostic value of advanced cardiac imaging is reflected in the 2015 ESC and AHA/ACC guidelines, which recommend combined ^{18}F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) for diagnosing prosthetic valve endocarditis but not for native valve endocarditis.[4,10]

In 2019, San et al[22] confirmed the rationale for this recommendation after evaluating FDG-PET/CT in 64 patients with native valve endocarditis and 109 patients with prosthetic valve endocarditis. FDG-PET/CT was found not only to be a better diagnostic tool for prosthetic valve endocarditis than for native valve endocarditis (sensitivity 83% vs 16%), but it was also better for predicting major cardiac events, infective endocarditis recurrence, and new embolic events ($P = .04$).

CARDIAC DEVICE-RELATED INFECTIONS

Diagnosing infective endocarditis is challenging in patients who have an implantable cardiac device, and TEE is superior to TTE.

In 1994, Vilacosta et al[23] used echocardiography to evaluate 10 patients with permanent transvenous pacemakers who were suspected of having infective endocarditis. TTE was positive for pacemaker lead vegetations in 2 of these patients, while TEE was positive in 7 patients.

In 2013, Narducci et al[24] conducted a prospective observational study in 162 patients comparing TEE with intracardiac echocardiography in diagnosing cardiac device-related infection. Intracardiac echocardiography had high diagnostic accuracy for detecting intracardiac masses (sensitivity 100%, specificity 82.8%, positive predictive value 65.6%, and negative predictive value 100%, $P < .001$). However, because this method is invasive and needs to be performed in the cardiac catheterization laboratory, it may not be appropriate for other types of infective endocarditis, for which TTE or TEE have sufficient diagnostic capacity.

PET/CT has also been explored for diagnosing infective endocarditis in patients with implantable cardiac devices.[25]

CAUSATIVE ORGANISMS

A variety of pathogens have been implicated in causing infective endocarditis. A prospective cohort study of 2,781 patients with infective endocarditis in 58 hospitals in 25 countries found the 5 most common pathogens to be:

- *S aureus* (31%)
- Viridans streptococci (17%)
- Enterococci (11%)
- Coagulase-negative staphylococci (11%)
- *Streptococcus bovis* (7%).

Rarer causative organisms include other streptococci, fungi, and HACEK organisms (*Haemophilus aphrophilus*, *Aggregatibacter* [previously *Actinobacillus*] *actinomycetemcomitans*,

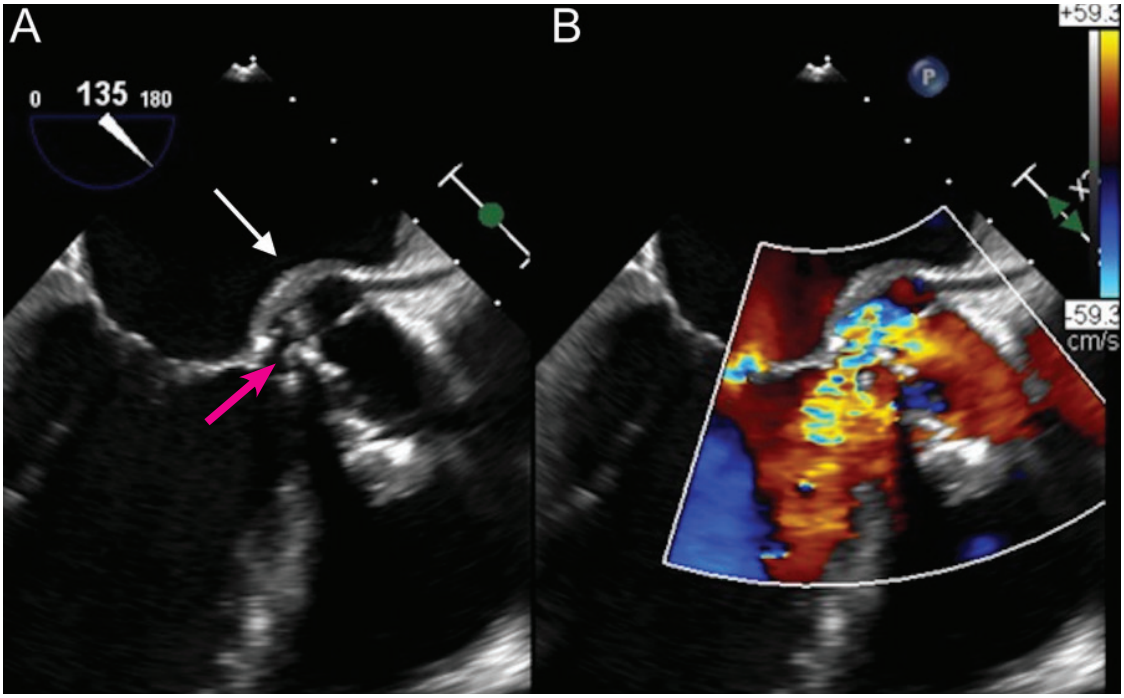

Figure 1. (A) Transesophageal echocardiography, mid-esophageal long-axis view, demonstrates a prominent aortic root abscess cavity (white arrow) posteriorly in a patient with a prosthetic aortic valve. Also note partial dehiscence of the aortic bioprosthesis (red arrow). (B) Color Doppler analysis demonstrates significant aortic regurgitation between the aortic bioprosthesis and the left ventricular outflow tract through the prominent abscess cavity.

Cardiobacterium hominis, *Eikenella corrodens*, and *Kingella kingae*).[2]

S aureus bacteremia

Infective endocarditis worsens the prognosis of *S aureus* bacteremia, and patients with an intracardiac device are at especially high risk of having infective endocarditis in the setting of *S aureus* bacteremia.[26]

Initial evaluation with TEE has been suggested for patients with *S aureus* bacteremia because of the high complication rate associated with failure of diagnosis in this setting, and the higher sensitivity and specificity of TEE than TTE alone.[27] However, the ESC guidelines recommend TTE as the first-line imaging in *S aureus* bacteremia, and a repeat investigation with TTE, TEE, or both within 7 to 10 days.[7,10] A 2014 study by Barton et al[27] found that more than half of patients (132 of 256) with *S aureus* bacteremia had an initially negative TTE, of which only 6 were subsequently diagnosed with infective endocarditis by TEE (negative predictive value 95% for TTE in *S aureus* bacteremia), suggesting that TTE may be satisfactory in follow-up of initially TTE-negative patients with uncomplicated *S aureus* bacteremia.

Figure 1 shows an aortic root abscess, a possible complication of *S aureus* bacteremia-associated infective endocarditis.

TTE is rapid, noninvasive, widely available, and highly specific

Enterococcal species

An estimated 3% to 10% of patients with enterococcal bloodstream infections develop infective endocarditis.[27] Unlike *S aureus* bacteremia, for which the 2015 AHA guidelines advise initially performing TEE, this is generally not recommended for enterococcal bacteremia.[4]

Bouza et al[28] proposed the NOVA score to identify those patients with enterococcal bacteremia with high enough risk of infective endocarditis to warrant TEE. The NOVA score consists of the following:

- Persistent bacteremia (defined as 3 of 3 positive blood cultures or the majority positive if more than 3) = 5 points

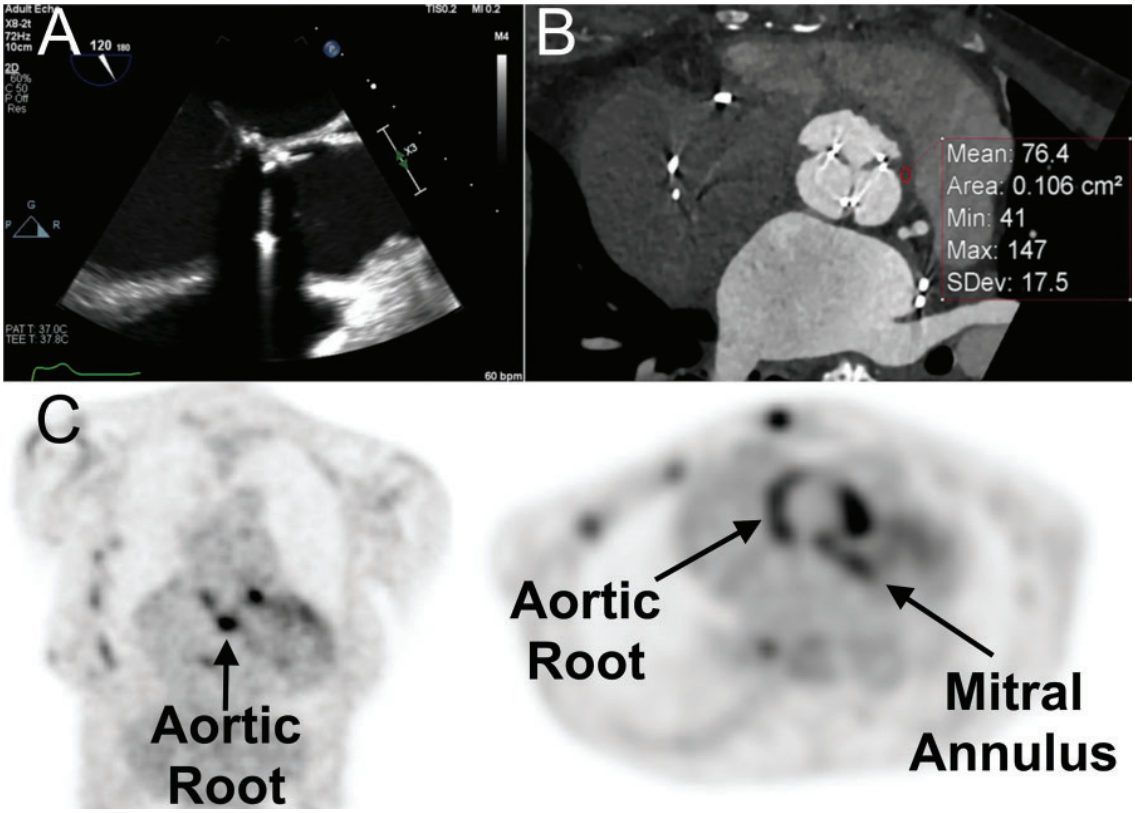

Figure 2. Utility of adjuvant advanced cardiovascular imaging—multidetector cardiac computed tomography (MDCT) and ^{18}F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT)—in the diagnosis of infective endocarditis. A 68-year-old woman with *Staphylococcus aureus* bacteremia in the setting of a bioprosthetic aortic valve developed fever and acute right lower limb pain. Initial transesophageal echocardiography (mid-esophageal long-axis view) showed no obvious vegetation associated with the bioprosthesis (A). Due to ongoing clinical suspicion for prosthetic aortic valve endocarditis, MDCT was performed (B) and, at the level of the aortic root, showed abnormal thickening with elevated Hounsfield units (mean: 76.4 units), highly suspicious for periprosthetic aortic root abscess. FDG-PET/CT (C), demonstrated abnormal increased activity at the aortic root and mitral annulus (arrows).

Perform TTE as soon as infective endocarditis is suspected, and also use TEE in most cases

- Unknown source of bacteremia = 4 points
- History of valve disease = 2 points
- Heart murmur auscultated = 1 point.

The authors concluded that a score of 4 points or more warrants TEE, with a sensitivity of 100% and specificity of 29% for detecting infective endocarditis.

In a retrospective cohort study, Dahl et al[29] evaluated a modified NOVA score (2 of 2 positive blood cultures earning 5 points, and all other criteria unchanged). Seventy-six of 78 patients with enterococcal infective endocarditis had a NOVA score of at least 4, translating into a sensitivity of 97% and a negative predictive value of 95%. The findings support the use of the NOVA score in identifying patients with a low risk of infective endocarditis for whom investigation with TTE may be sufficient. Timing for a repeat echocardiogram, however, is recommended at 7 to 10 days regardless, according to ESC guidelines for *S aureus* and *Enterococcus faecalis* bacteremias.[7]

ALTERNATIVE IMAGING METHODS

With advances in cardiovascular imaging, evaluating infective endocarditis is no longer limited to conventional echocardiography and may also include other methods, eg, MDCT, FDG-PET/CT, and other functional imaging (**Figure 2**).

Echocardiography is limited in that early vegetations are often difficult to detect on TTE and TEE if their size is below the resolution of the transducer. Also, small vegetations can be hard to differentiate from degenerative valvular thickening or calcification.[8] The ESC guidelines provide some guidance for using alternative imaging methods, such as MDCT and FDG-PET/CT, to increase the sensitivity of the Duke Criteria, but evidence is limited.[10] Despite the growing use of alternative imaging modalities such as MDCT and PET/CT, few studies exist comparing them with TTE and TEE for diagnosing infective endocarditis. As adjuvant imaging modalities become more widely used, more prospective trials are needed to increase the evidence base.

3-D TEE has advantages over 2-D TEE

A 2014 study by Berdejo et al[30] compared 3-D TEE with conventional 2-D TEE in 60 patients with a definite diagnosis of infective endocarditis as demonstrated by vegetations seen on 2-D TEE. 2-D TEE underestimated the size of vegetations: the difference in maximum length between 3-D and 2-D TEE was 3.2 mm (95% CI 2.1–4.2 mm).

3-D TEE has potential advantages in evaluating paravalvular extension of infection, valve perforation, and prosthetic valve dehiscence.[10] However, high-quality 3-D echocardiography relies on optimal 2-D imaging, from which the 3-D images are generated.

MDCT is better in some situations

Some studies have found MDCT to be better than echocardiography at identifying infective endocarditis. A review by Goddard et al[31] found several studies showing MDCT to be equivalent or superior to echocardiography for identifying prosthetic vegetations, abscesses, pseudoaneurysms, and dehiscence.

A 37-patient study by Feuchtner et al[32] found that MDCT detected valvular abnormalities in 28 of 29 patients with confirmed infective endocarditis, with a sensitivity of 97% and specificity of 88%. Moreover, MDCT detected paravalvular abscesses and pseudoaneurysms that were not detected by TEE in 3 patients.

MDCT may be superior in these scenarios, especially for evaluating paravalvular extension of infections. However, for typical findings, especially for detecting smaller, mobile vegetations, echocardiography with higher temporal resolution remains the preferred imaging method.[31] In a study comparing MDCT with TEE in 75 patients with confirmed infective endocarditis, vegetations smaller than 10 mm were underdiagnosed by MDCT compared with TEE (detection rate 52.8% vs 94.4%).[33] Moreover, MDCT assessment is dependent on the quality of the valve images and requires dedicated protocols. For instance, it may be difficult to interrogate the tricuspid valve precisely by MDCT.

FDG-PET/CT has an emerging role

Nuclear imaging techniques are becoming increasingly important for diagnosing infective endocarditis, especially for patients with equivocal TTEs or a negative TTE but a high clinical suspicion of infective endocarditis. FDG-PET/CT has been reported to reduce the rate of misdiagnosed infective endocarditis by detecting peripheral embolic and metastatic infectious events.[34] Studies have shown its promising role as a diagnostic tool for infective endocarditis, particularly if related to a prosthetic valve or cardiac device; in such settings, FDG-PET/CT has been found to detect periprosthetic abscesses not identified by echocardiography.[25,35,36]

TEE is superior to TTE for evaluating patients with an implantable cardiac device

A 2020 meta-analysis of 1,358 patients found the pooled sensitivity of FDG-PET/CT to be 0.86 in infective endocarditis involving a prosthetic valve, 0.72 involving a cardiac device, and only 0.31 in native valve infective endocarditis.[36]

This imaging technique may also prove useful for monitoring clinical response to antimicrobial treatment.[37]

However, drawbacks include limited evidence of its cost-effectiveness and limited availability, only in tertiary centers with access to PET/CT scanners and appropriate imaging team support.[37] In clinical practice, equivocal findings with mild uptake result in clinical ambiguity as to whether an infection is present. Due to limited resolution and valve mobility, the technique may not be sensitive in detecting vegetations smaller than 5 mm on native valves.[38] In addition, other diseases associated with increased metabolic activity, including thrombi, atherosclerotic plaques,

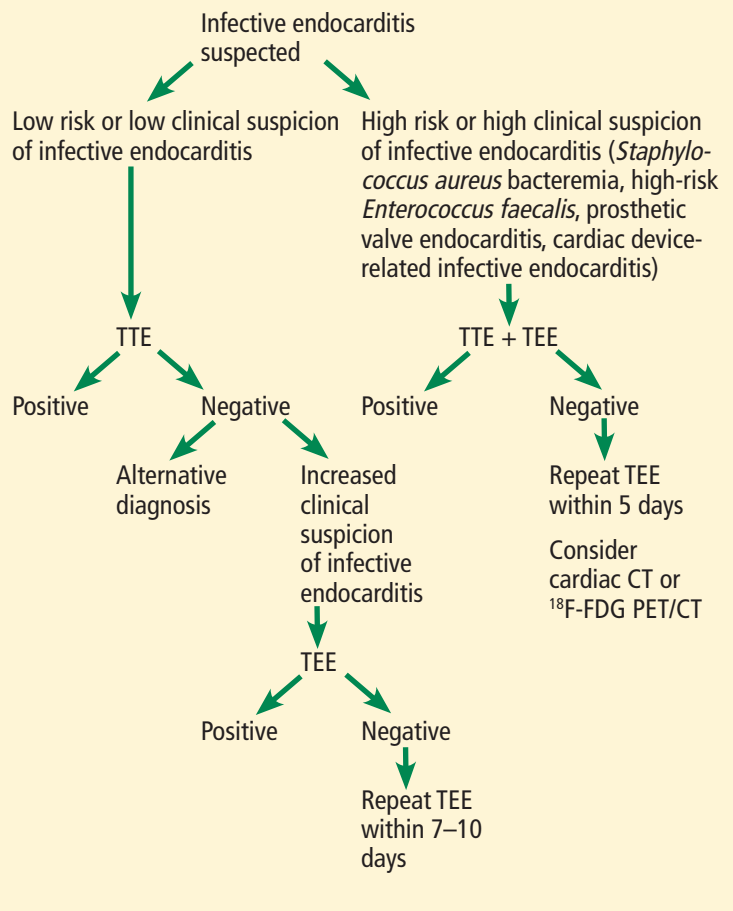

Figure 3. A proposed diagnostic algorithm for infective endocarditis.

TEE = transesophageal echocardiography; TTE = transthoracic echocardiography

sarcoidosis, and primary and metastatic cardiac tumors, may cause false-positive findings, due to focal FDG uptake in the absence of infection.[37]

OUR ALGORITHM FOR EVALUATING SUSPECTED INFECTIVE ENDOCARDITIS

We propose a diagnostic pathway for evaluating suspected infective endocarditis based on the current literature and ESC and AHA/ACC guidelines (**Figure 3**). First, patients should be risk-stratified to guide the choice of initial imaging method. Per AHA/ACC guidelines, patients with persistent *S aureus* or *E faecalis* bacteremia, prosthetic valves, or cardiac devices should be characterized as high risk. They may require TEE imaging as a first-line investigation due its higher diagnostic accuracy. If initial TTE is negative and bacteremia persists in high-risk patients, then TEE should be performed within 5 days and consideration given to adjuvant imaging modalities. MDCT can be used to better visualize prosthetic vegetations, abscesses, pseudoaneurysms, and dehiscence. FDG-PET/CT may be used for patients with prosthetic valves or cardiac implantable electronic devices.

If a low-risk patient has a negative TTE, the clinician should look for alternative diagnoses, ie, other than infective endocarditis. If clinical suspicion for infective endocarditis increases during the clinical evaluation, TEE should be conducted. If this yields a negative result, TEE should be repeated in 7 to 10 days.

CASE CONCLUDED

Due to ongoing clinical suspicion for prosthetic aortic valve infective endocarditis, despite apparently unremarkable echocardiographic imaging, adjuvant advanced imaging with dedicated cardiac CT and FDG-PET/CT were pursued (**Figure 2**). These studies helped confirm the diagnosis of prosthetic aortic valve infective endocarditis. The patient underwent re-do cardiac surgery successfully. At follow-up, the patient completed the course of antimicrobial therapy and was clinically well. ■

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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REVIEW

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Male and female pattern hair loss: Treatable and worth treating

ABSTRACT

Pattern hair loss is the most common type of hair loss in both men and women. Scalp hair is typically affected in a characteristic distribution without other scalp or dermatologic findings. Early recognition and treatment can help halt its progression to preserve as much hair as possible. Both pharmacologic and nonpharmacologic treatments have proven helpful.

KEY POINTS

Male and female pattern hair loss is a nonscarring, progressive form of alopecia that typically affects the temporal, frontal, and vertex scalp in men and central scalp in women.

The process can begin soon after puberty, and the resulting hair loss negatively affects quality of life and self-image.

Pattern hair loss is commonly diagnosed with a thorough history; physical examination of the face, scalp, and nails; the hair-pull test; dermoscopy; and laboratory testing. A hair biopsy may be of value for clinically challenging cases.

Topical minoxidil and oral finasteride are first-line treatments for male pattern hair loss and topical minoxidil is the first-line therapy for female pattern hair loss, but there are a number of other off-label pharmacologic and nonpharmacologic treatments.

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PATTERN HAIR LOSS is a progressive, nonscarring form of hair loss characterized by gradual loss of terminal hair and follicular miniaturization to vellus hair fibers on the scalp in a characteristic distribution. It is the most common form of hair loss in both men and women and has psychosocial effects, including stress and diminished quality of life.

This review focuses on clinical presentation, diagnosis, and treatment of pattern hair loss.

MANY NAMES FOR IT

This condition goes by many names, such as androgenetic alopecia, androgenic alopecia, male balding, male pattern hair loss, female pattern alopecia, diffuse alopecia in women, and hereditary alopecia. The term "androgenetic alopecia" was used in the past, recognizing the hormonal and hereditary influences underlying the condition in men.

As our understanding of both the pathophysiology and phenotypic expression expanded, so did the collection of terms used to identify this disorder. Newer terminology developed to express the different patterns of presentation in men and women and the uncertain role, and frequent absence, of androgen excess in women. *Male pattern hair loss* and *female pattern hair loss* are now the favored terms.

GENES PLAY A ROLE

Male and female pattern hair loss are polygenic conditions, which explains their high prevalence and variable phenotypic expression.[1] Epigenetic modifications may alter genetic susceptibility.[1]

Interestingly, genetic variations associated with the androgen receptor gene (*AR*) have

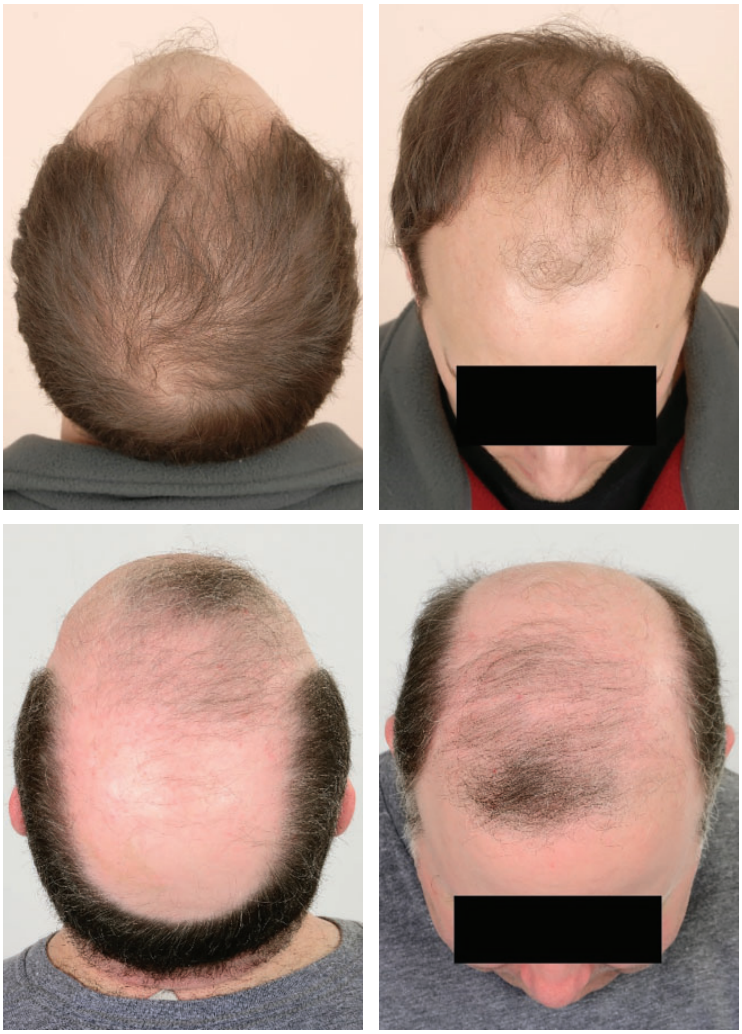

Figure 1. Male pattern hair loss.

been linked to development of male pattern hair loss, but genes for aromatase (*CYP19A1*), estrogen receptor-a (*ESR1*), type I 5-alpha reductase (*SRD5A1*), and insulin-like growth factor 2 (*IGF-2*) do not have any established association with it.[1]

Research into genetic associations with female pattern hair loss is less extensive and robust than that of male pattern hair loss. Studying the relationship between female pattern hair loss and *AR* has proven difficult, since *AR* is located on the X chromosome, which undergoes X inactivation in women.[1] An allelic variant of *CYP19A1* was associated with a predisposition to female pattern hair loss in a genome-wide association study.[2]

LINKED TO ANDROGEN EXCESS IN MEN

Androgens are considered necessary for male pattern hair loss to develop. The condition typically begins after the start of puberty, which is marked by a striking increase in androgen levels. Dihydroxytestosterone, a potent metabolite of testosterone synthesized in a reaction catalyzed by 5-alpha reductase in the peripheral target organs, hair follicle, and sebaceous glands, plays a role in normal hair growth and male pattern hair loss development in androgen-sensitive areas such as the vertex and frontal scalp, beard, axilla, pubis, and extremities. Dihydroxytestosterone assists normal hair growth in these areas, but elevated cellular levels of androgen receptors and 5-alpha reductase[3] and increased production of dihydroxytestosterone[4] have been documented in cases of male pattern hair loss. No cases of male pattern hair loss have been documented in men with 5-alpha reductase deficiencies.[5]

UNCLEAR RELATIONSHIP WITH HORMONES IN WOMEN

The relationship between androgens and female pattern hair loss is less clear. Female pattern hair loss has been observed in women with high androgen levels,[6] but it has also been documented in a patient with complete androgen insensitivity syndrome.[7] Additionally, most women with female pattern hair loss have normal testosterone levels and lack clinical manifestations of hyperandrogenemia.[6]

The role of circulating estrogens in the development of female pattern hair loss is also unclear. The prevalence of hair loss increases after menopause. Evidence is conflicting regarding whether estrogen stimulates or inhibits the hair follicle.[1]

CAN BEGIN EARLY

Pattern hair loss in men and women begins soon after puberty. Thinning of hair and nonscarring loss of terminal hairs, resulting in a decrease in hair density, generally progress slowly over years. The scalp is healthy without associated symptoms.

In men, hair loss typically affects the central scalp, including the midfrontal, temporal, and vertex regions (**Figure 1**). The 7-stage Hamilton-Norwood scale is commonly used

to classify male pattern hair loss.[8] However, in some men, hair loss does not follow this typical progression or is more severe in particular areas.

In women, the characteristic distribution of hair loss is different. Female pattern hair loss has 2 general distributions: diffuse thinning across the central scalp and the characteristic "Christmas tree" pattern observed along the midline part of the hair due to prominent hair thinning towards the front of the scalp with minimal involvement of the hairline (**Figure 2**).[9,10] The frontal hairline is less likely to be involved, but bitemporal thinning is common. The 3-grade Ludwig scale is commonly used to characterize female pattern hair loss.[11]

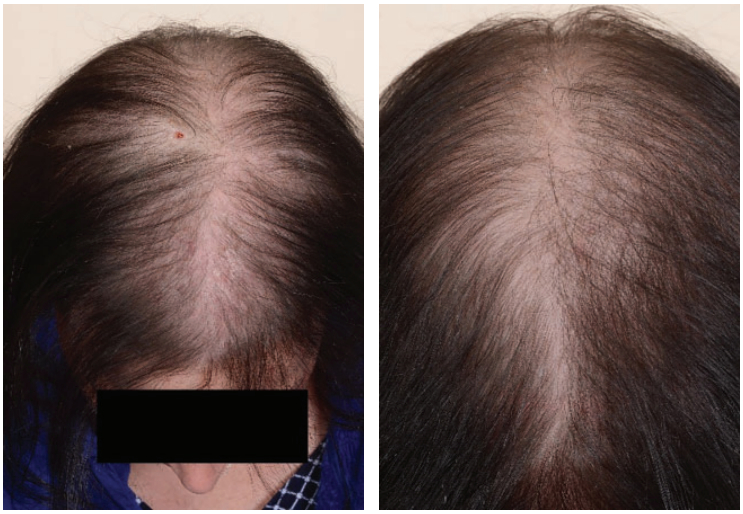

Figure 2. Female pattern hair loss.

A CLINICAL DIAGNOSIS

Pattern hair loss is typically diagnosed clinically (**Table 1**).

History

A thorough history should be elicted, including age of onset of hair loss, time course, severity, hair loss distribution, progression (ie, periods of shedding), and accompanying symptoms. For women, a gynecologic history may help uncover an underlying cause such as polycystic ovarian syndrome or hyperandrogenism. The patient should be asked about any family history of hair loss, metabolic syndromes (eg, diabetes mellitus), and androgen excess; medications; and medical history.

Conditions that worsen hair loss, including iron deficiency, thyroid dysfunction, and nutritional deficiencies, should be considered and managed to improve treatment results.

Physical examination

A complete skin evaluation should be conducted, including the face, scalp, and nails.

When examining the scalp, note the distribution of hair loss, the caliber of hairs, and other clinical features. Male pattern hair loss typically presents as a receding hairline and hair miniaturization on the frontal and vertex scalp. In women, the vertex and midfrontal scalp are commonly affected, as described above. Hair loss can be assessed by comparing the hair part of the central scalp with that of the occipital scalp, which is generally spared. Hair miniaturization can be seen better using a sheet of paper as a backdrop and comparing the caliber of adjacent hair shafts.

Inflammation, scarring, or scaling of the scalp suggests a different diagnosis, as pattern hair loss is usually unaccompanied by these signs. Nevertheless, seborrheic dermatitis is more prevalent in people with pattern hair loss,[12] so male and female pattern hair loss can present with another scalp condition. Seborrheic dermatitis is often associated with seborrhea (oily scalp) which is a result of androgen stimulation of the sebaceous glands.

Nail involvement (eg, pitting, trachyonychia, and longitudinal ridging) and patchy hair loss in nonscalp regions (eg, the eyebrows) are inconsistent with the diagnosis of male or female pattern hair loss.

Male pattern and female pattern hair loss are polygenic conditions

Hair-pull test

The hair-pull test, which is useful in detecting active hair loss, is performed by grasping 50 to 60 hairs close to the scalp with the thumb, index, and middle fingers and slowly pulling. If 6 or more hairs come loose, hair loss is likely active.

Extracted hair can be examined under the microscope to characterize the type (eg, broken or dystrophic) and the phase (eg, telogen [resting] or anagen [growth]). A study by McDonald et al[13] suggested that neither washing nor brushing the hair affects results of the hair-pull test. In pattern hair loss, the hair-pull test is generally negative, though it can be positive early in the process on the vertex or midfrontal scalp.

Dermoscopy

Examination of the scalp with a dermatoscope can reveal epidermal and dermal structures undetectable with the naked eye. Dermoscopic findings of diversity in hair diameter, yellow dots (sebaceous glands), perifollicular pigmentation, and lack of scarring are consistent with the diagnosis of male or female pattern hair loss. Small focal areas with complete hair loss may be observed, and skin pigmentation in these areas may vary due to sun exposure.[14]

Scalp biopsy

Though generally not required, a scalp biopsy can be helpful when the clinical picture is unclear or coexisting scalp conditions are suspected. Two 4-mm punch biopsies are taken in the direction of the hair shaft, allowing for transverse and vertical sectioning.

Histologic features of male and female pattern hair loss include terminal hair miniaturization (hair shaft diameter ≤ 0.03 mm), increased percentage of telogen hairs (15%–20%), decreased ratio of terminal to vellus or vellus-like hairs (1.9:1 in men and 1.5:1 in women), and reduced total number of hairs per unit area.[10]

Androgens are considered necessary for male pattern hair loss

Laboratory testing

Thyroid-stimulating hormone and iron studies (including serum ferritin, serum iron, and total iron binding capacity) can be helpful in assessing men and women with pattern hair loss.[10]

Women with clinical manifestations of androgen excess such as hirsutism, adult acne, irregular menses, and acanthosis nigricans should undergo a laboratory workup for hyperandrogenemia.[10] This includes free or total testosterone with or without dehydroepiandrosterone sulfate.[10] Measuring serum prolactin can also be considered for women presenting with concomitant galactorrhea or elevated testosterone.[10]

A complete blood cell count and comprehensive metabolic panel are also routinely done. Because many people are on restricted diets, a nutrient screen is suggested that includes iron saturation, ferritin, zinc, and vitamin D levels.

DIFFERENTIAL DIAGNOSIS

Other forms of alopecia that may present similarly to male and female pattern hair loss include telogen effluvium, alopecia areata, traction alopecia, trichotillomania, central centrifugal cicatricial alopecia, lichen planopilaris, and frontal fibrosing alopecia (**Figure 3**).[15,16]

Telogen effluvium, a condition of noninflammatory, diffuse hair loss, is often difficult to distinguish from female pattern hair loss. A thorough history is very important, as there is generally an inciting trigger such as psychological stress, childbirth, weight loss, or medications (eg, interferons, antihyperlipidemic medications, derivatives of retinol, anticoagulants) that precedes telogen effluvium by a few months. Hair loss generally occurs over the entire scalp, occasionally most prominently in the temporal areas. The hair-pull test is positive, with increased shedding of telogen hairs when telogen effluvium is active. Of note, telogen effluvium and female pattern hair loss can coexist in the same patient.

Alopecia areata commonly presents as focal, smooth patches of hair loss, which spontaneously regrow (**Figure 3A**). Rarely, it can present as diffuse hair loss with widespread decreased hair density (diffuse alopecia areata) or as larger patches of hair loss on the frontal, parietal, and temporal scalp (ophiasis inversus), mimicking female and male pattern hair loss, respectively. Alopecia areata totalis and alopecia areata universalis are characterized by more severe hair loss; alopecia areata totalis represents total loss of scalp hair, whereas alopecia universalis has more extensive hair loss including the face and body in addition to the scalp (**Figure 3B**).

The onset is usually sudden with prominent shedding, characteristically an anagen effluvium with dystrophic anagen hairs. Telogen hairs are typically lost during chronic shedding. These patients commonly have a positive family history of alopecia areata.[17] Additionally, nail involvement, such as pitting, longitudinal fissuring, and lunula reddening, occur in 10% to 20% of patients with alopecia areata.[18] The hair-pull test is positive in patients who are actively shedding.

Traction alopecia is a result of chronic (prolonged or repeated) tension on the hair, often from hairstyles. Hair loss along the hairline is common (**Figure 3C**). A thorough his-

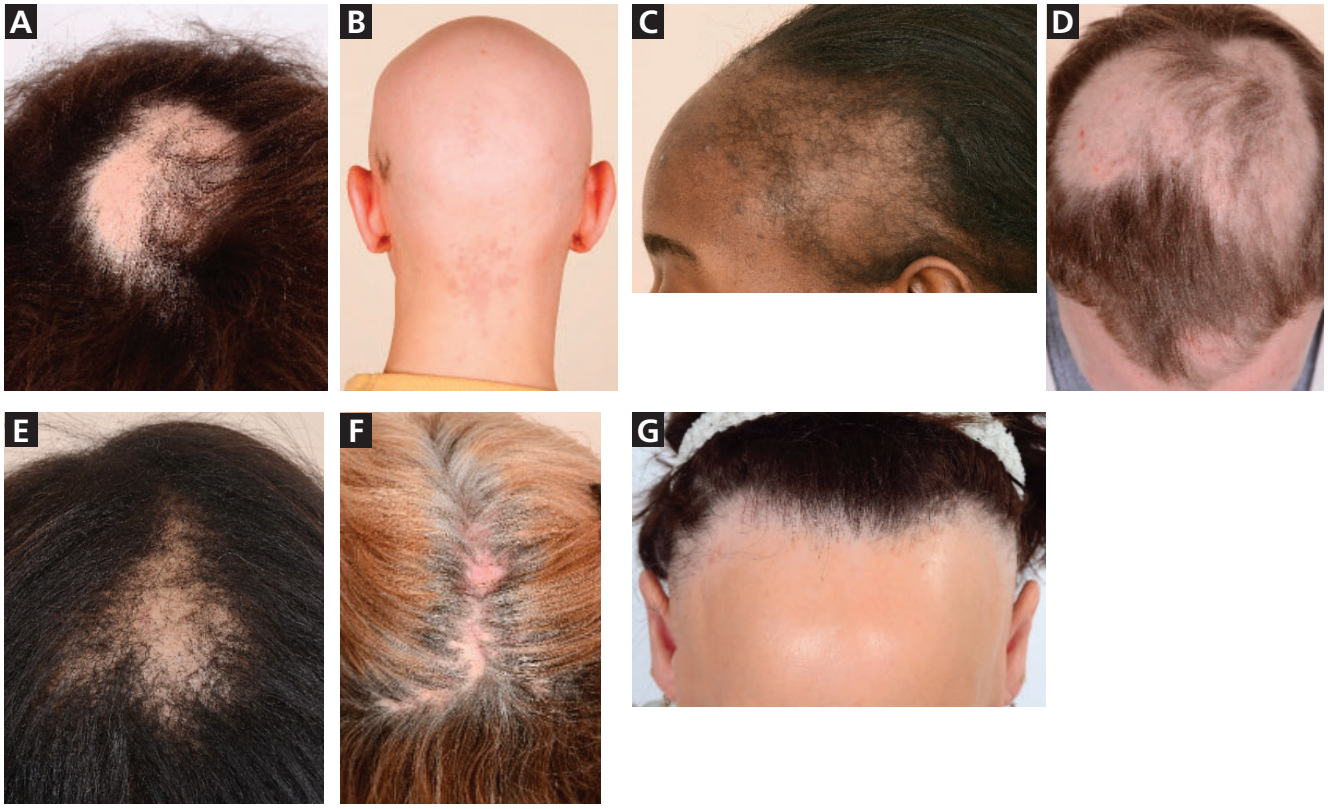

Figure 3. Differential diagnosis for pattern hair loss. A, patchy alopecia areata; B, alopecia totalis; C, traction alopecia; D, trichotillomania; E, central centrifugal cicatricial alopecia; F, lichen planopilaris; G, frontal fibrosing alopecia.

tory can be helpful with the diagnosis.

Trichotillomania is a psychiatric condition in which patients repeatedly pull at their hair. Hair loss can occur on different portions of the body with hairs of different lengths as a result of episodes of hair pulling or variations in breakage point along the hair shaft within the same episode. Hair loss occurs in bizarre patterns (**Figure 3D**). The eyebrows, eyelashes, and pubic hair can be involved.

Central centrifugal cicatricial alopecia, most commonly affecting women of African descent, is a form of scarring alopecia that often affects the vertex of the scalp. It is associated with the gene *PAD13*, which encodes an enzyme, type III peptidyl arginine deiminase, critical for hair shaft formation.[19]

Usually, central centrifugal cicatricial alopecia first presents as a patch of hair thinning that progresses to more severe hair loss expanding from the center of the lesion. It increases in size in a centrifugal fashion, with the center most severely affected with loss of hair follicles (**Figure 3E**). Central centrifugal cicatricial alopecia can be differentiated from female pattern hair loss by visible loss of the follicular ostia. Additionally, it can present with other signs and symptoms on the scalp, including pustules, erythema, tenderness, and pruritus.

Lichen planopilaris and frontal fibrosing alopecia are uncommon inflammatory scarring alopecias that have similar histologic findings but dissimilar clinical presentations. Classic lichen planopilaris presents as small to large areas of patchy hair loss, frequently affecting the vertex or parietal scalp (**Figure 3F**). Hair loss in lichen planopilaris may present similarly to central centrifugal cicatricial alopecia, but there are no vellus hairs in lichen planopilaris.[20] Nail, cutaneous, and mucosal involvement can occur.

Frontal fibrosing alopecia results in recession of the hairline in a bandlike distribution in women (**Figure 3G**), with perifollicular erythema, and follicular hyperkeratosis. Unlike female pattern hair loss, frontal fibrosing alo-

TABLE 1

Workup of pattern hair loss in men and women

History
Age of onset, time course, severity, hair loss distribution, progression (periods of shedding), accompanying symptoms
Medical history
Gynecologic history
Medication and supplement list
Family history of hair loss, androgen excess, and metabolic disease

Physical examination
Distribution of hair loss
Hair caliber and texture
Clinical features of scalp
Nail changes

Hair-pull test

Dermoscopy

Scalp biopsy

Laboratory testing
Complete blood cell count
Comprehensive metabolic panel
Antithyroid antibody testing
Thyroid-stimulating hormone with or without free thyroxine
Iron evaluation (serum ferritin, serum iron, total iron-binding capacity)
Free and/or total testosterone
Dehydroepiandrosterone sulfate
Serum prolactin
Zinc
Hydroxy-25 vitamin D

pecia often affects the eyebrows and temporal scalp and can result in complete and permanent hair loss.

LOWER SELF-ESTEEM

Pattern hair loss can lead to negative feelings in both men and women and can contribute to stress, decrease body image satisfaction, damage self-esteem, and diminish quality of life, especially among women and individuals seeking treatment.[21] Patient and physician perceptions of disease severity may diverge, underlying the importance of attending to the psychosocial and psychoemotional status of these patients.[22]

LOSS IS PROGRESSIVE

Pattern hair loss is progressive, leaving patients with diminished hair density. Male pattern hair loss can result in complete loss of hair coverage in particular areas, whereas female pattern hair loss rarely advances to baldness.

Response to pharmacologic treatment varies, but it is important to recognize pattern hair loss and initiate treatment early in the disease process to try to prevent further hair loss and promote some degree of hair regrowth.

TREATMENT

The goal of treatment of pattern hair loss is to promote regrowth of hair to improve scalp coverage and to prevent or slow further hair thinning and loss. Topical minoxidil and oral finasteride are the first-line treatments for male pattern hair loss, and topical minoxidil is the first-line treatment for female pattern hair loss. However, there are a number of alternatives. Detecting and treating comorbidities such as androgen excess and nutritional deficiencies is helpful in maintaining hair growth.

Minoxidil

Mechanism of action. Through an unclear mechanism, minoxidil enhances hair growth by enlarging miniaturized hair follicles, extending anagen, and shortening telogen.[23]

US Food and Drug Administration (FDA) approval. Minoxidil is FDA-approved for treating both male and female pattern hair loss.

Administration. Topical minoxidil is available over the counter in 2% and 5% solutions and 5% foam in the United States. Patients should apply 1 mL of 5% solution or half a cap of 5% foam once a day directly to involved areas of the scalp (not the hair) when dry. Treatment should be assessed for efficacy after 1 year of use, but results may be observed sooner.

Efficacy in men. In a 48-week, double-blind, placebo-controlled, randomized trial, 5% minoxidil solution was superior to 2% solution in terms of patient perception of hair growth and treatment benefit, investigator perception of hair growth, and nonvellus hair count.[24] Response time was also shorter with the 5% solution. Both the 2% and the 5% topical minoxidil solutions were superior to placebo.

Foam has not been directly compared with liquid solutions. Compared with placebo, 5% minoxidil foam increased the hair count and improved hair loss as assessed by the patient

and physician.[25]

Individual response to treatment with minoxidil varies, and hair regrowth can be lost after stopping.

Efficacy in women. A meta-analysis found that topical minoxidil was effective and safe for treating female pattern hair loss, with no significant difference in efficacy and safety between different concentrations.[26] Topical minoxidil is an effective treatment for women regardless of androgen status and age.[10]

Side effects. Minoxidil stimulates telogen follicles to enter anagen, so transient hair shedding may occur when initiating therapy. Contact dermatitis and hypertrichosis are common side effects. Compared with 2% topical minoxidil, 5% preparations are more likely to cause local pruritus and irritation.[25]

Finasteride

Mechanism of action. Finasteride, a competitive inhibitor of type II 5-alpha reductase, decreases production of dihydroxytestosterone. Oral finasteride reduces scalp dihydroxytestosterone levels by approximately 60% to 70%, depending on the dosage.[26]

FDA approval. Finasteride is FDA-approved for treating male pattern hair loss, but not female pattern hair loss.

Administration. Men with male pattern hair loss can be treated with finasteride 1 mg daily. Treatment should be assessed for efficacy after 1 year of use, but results may be observed sooner.

Efficacy in men. Finasteride has been shown to increase the hair count, physician-assessed hair coverage, and hair mass compared with placebo.[27,28]

A systematic review of the efficacy of finasteride in men with male pattern hair loss found that 5.6 patients need to be treated short-term, and 3.4 patients need to be treated long-term, for 1 patient to perceive an improvement.[27] There was a 20% absolute increase in patient-perceived improvement in the short term and a 30% absolute increase in the long term.[27] Longer treatment with finasteride promotes greater therapeutic success.

Similar to minoxidil, response to finasteride varies, and hair regrowth can be lost after the medication is discontinued.

Efficacy in women. A double-blind, placebo-controlled, randomized multicenter trial found finasteride 1 mg to be ineffective in postmenopausal women with female pattern hair loss at 12 months.[29] However, higher doses of finasteride daily can be effective in cases of female pattern hair loss associated with hyperandrogenemia.[30]

Side effects. In a systematic review, the only adverse effect associated with finasteride treatment was erectile dysfunction, with an absolute increase in risk of approximately 1.5%.[27] Approximately 1 in every 80 men treated with finasteride experiences this side effect. Stopping finasteride generally leads to resolution of erectile dysfunction, but sexual dysfunction can persist in some patients.

Other reported side effects of finasteride include decreased libido, gynecomastia, testicular pain, and depression.

Considerations. Finasteride can result in lower prostate-specific antigen levels in men, which should be taken into consideration when interpreting laboratory results. Due to hepatic metabolism of finasteride, precautions should be taken with patients with liver disease. With chronic treatment, finasteride may cause mild to moderate elevations in serum liver enzymes, but this is usually self-limiting and rarely requires dose modification or drug discontinuation.[31]

Consider conditions that worsen hair loss: eg, iron deficiency, thyroid dysfunction, and nutritional deficiencies

Dutasteride

Dutasteride, a potent type I and type II 5-alpha reductase inhibitor, is used to treat benign prostatic hyperplasia, but is also prescribed as an off-label treatment for pattern hair loss.

A randomized control trial[32] in 416 men with male pattern hair loss demonstrated that dutasteride 2.5 mg was superior to finasteride 5 mg in terms of increasing hair count over 24 weeks. Additionally, a meta-analysis[33] found that finasteride and dutasteride had similar efficacy in treating pattern hair loss.

Latanoprost, bimatoprost

Latanoprost is a prostaglandin F2 analogue that extends the anagen phase.[34] A double-blind, placebo-controlled, randomized trial in 16 men demonstrated an increase in hair density when latanoprost 0.1% was applied to a small area of the scalp.[35]

Bimatoprost is also being investigated as a potential treatment for pattern hair loss.

Ketoconazole, zinc shampoo

Ketoconazole, an antifungal medication that has anti-inflammatory and antiandrogenetic properties, can be used to treat seborrheic dermatitis and dandruff.[36] It was found to reduce inflammation in pattern hair loss and to benefit women with hyperandrogenemia and female pattern hair loss when used as a 2% shampoo.[37]

Over-the-counter zinc-containing shampoos have a similar mechanism of action and therapeutic effect.

Spironolactone

Spironolactone competitively inhibits the androgen receptor and also inhibits ovarian production of androgens. Of the antiandrogen drugs used off-label, it is the one most commonly used. It has been used to treat female pattern hair loss for over 2 decades and has a good safety profile.[37] An open-label trial[38] showed that spironolactone 200 mg daily improved hair regrowth in 44% of patients at 12 months, which was comparable to cyproterone acetate.

Cyproterone acetate

Other forms of alopecia may present similarly to male and female pattern hair loss

Cyproterone acetate is a progesterone derivative that prevents dihydroxytestosterone from binding to the androgen receptor and inhibits release of follicle-stimulating hormone and luteinizing hormone, thereby reducing testosterone levels. It is available combined with ethynyl estradiol as an oral contraceptive in many countries, but is not approved in the United States.

Platelet-rich plasma

Platelet-rich plasma is an autologous preparation of plasma with platelets, growth factors, and cytokines. It was initially used during hair transplantation procedures, with mixed results. Recently its use by itself has been explored to treat pattern hair loss. Preliminary evidence suggests that platelet-rich plasma may be advantageous in hair regrowth.[39] Side effects include redness and pain at injection site and pinpoint bleeding.

Low-level laser therapy

Low-level laser therapy is an FDA-approved treatment for pattern hair loss. The mechanism by which it improves hair loss is unclear, but it may stimulate follicular stem cells or keratinocytes, increase blood flow, promote mitosis, increase cell metabolism, and have anti-inflammatory effects.[40] Two double-blind, sham device-controlled, randomized trials demonstrated that low-level laser therapy increased hair density over 24 to 26 weeks of treatment, although differences global improvement ratings were not significant in one of the trials.[41,42]

Microneedling

Rolling fine needles over the skin causes minor physical trauma to the stratum corneum that incites wound healing. A randomized controlled trial demonstrated promising results with microneedling as an adjuvant to drug treatment for pattern hair loss.[43] Side effects of the procedure include pain and pinpoint bleeding.

Cosmetic aids

Nonmedical options allow patients to manage the appearance of thinning hair. Scalp colorants, including powders, lotions, and hair sprays, can reduce the color contrast between the skin and hair, camouflaging the scalp. The scalp can also be covered with wigs, hair extensions, or hair pieces.

Hair transplants

Follicles can be transplanted from an unaffected area of the scalp, commonly the occiput, where there are more than 40 follicular units/cm^3, to affected areas to create a permanent improvement in hair coverage. Young patients or patients with vertex involvement are not ideal candidates for this procedure due to the high likelihood of continued progression.[10] A large number of grafts, 1,000 to 2,000 follicles, can be transplanted in a single session. Additional transplantation sessions are generally scheduled at least 6 months apart, as it takes 5 to 6 months for results to be established.[10]

Pharmacologic treatment, such as oral finasteride, can be used in conjunction with hair transplantation before and after sessions to prevent hair miniaturization and loss of nontransplanted hair follicles.[44]

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Frequently asked questions about managing cancer pain: An update

ABSTRACT

Most patients with cancer experience pain at some point in the disease course due to the disease itself or its treatment, or both. Pain management can involve pharmacologic (nonopioid medications, adjuvants, and opioids) and nonpharmacologic (radiation therapy, interventional procedures) therapies. This article provides a treatment approach to reduce pain for patients with cancer and improve their quality of life.

KEY POINTS

- Cancer pain affects patients throughout the disease trajectory.
- The typical pharmacologic regimen for treating patients with cancer pain consists of an assortment of nonopioid analgesics, adjuvant pain medications, and opioids.
- Early consideration of radiation therapy and various interventional pain management procedures can optimize pain control and preclude escalation of opioids.
- New or worsening pain in patients with a history of cancer requires thorough assessment for cancer recurrence or progression.

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Cancer-related pain, resulting from the disease itself, its treatment, or both, is one of the disease's most agonizing symptoms, severely diminishing quality of life. A review of 52 studies published from 2005 to 2014, with 32,261 patients, concluded that 50.7% of patients with cancer experienced pain.[1] In those who completed curative treatment, the prevalence of pain was 39.3%, in those receiving anticancer therapy it was 55%, and in those with advanced, metastatic or terminal disease it was 66.4%.

Because cancer-related pain occurs throughout the course of the disease, primary care providers are likely to be called on to manage cancer pain, either in the outpatient or inpatient setting. Whether the provider is caring for a patient around the time of diagnosis, during treatment, at the terminal phase, or in survivorship, effective treatment of cancer pain helps patients achieve optimal quality of life. Knowledge of therapeutic approaches and both pharmacologic and nonpharmacologic alternatives may also assist clinicians in treating patients before partnering with specialists, such as those in oncology, palliative medicine, and pain management.

In an earlier article in this journal, Induru and Lagman[2] stressed that effectively managing cancer pain can lead to overall improvement in patient satisfaction and quality of life. They explored the use of drugs such as opioids and adjuvant pain medications and nonpharmacologic measures such as acupuncture, massage therapy, and music therapy. This article builds on the previous review and features novel drugs and

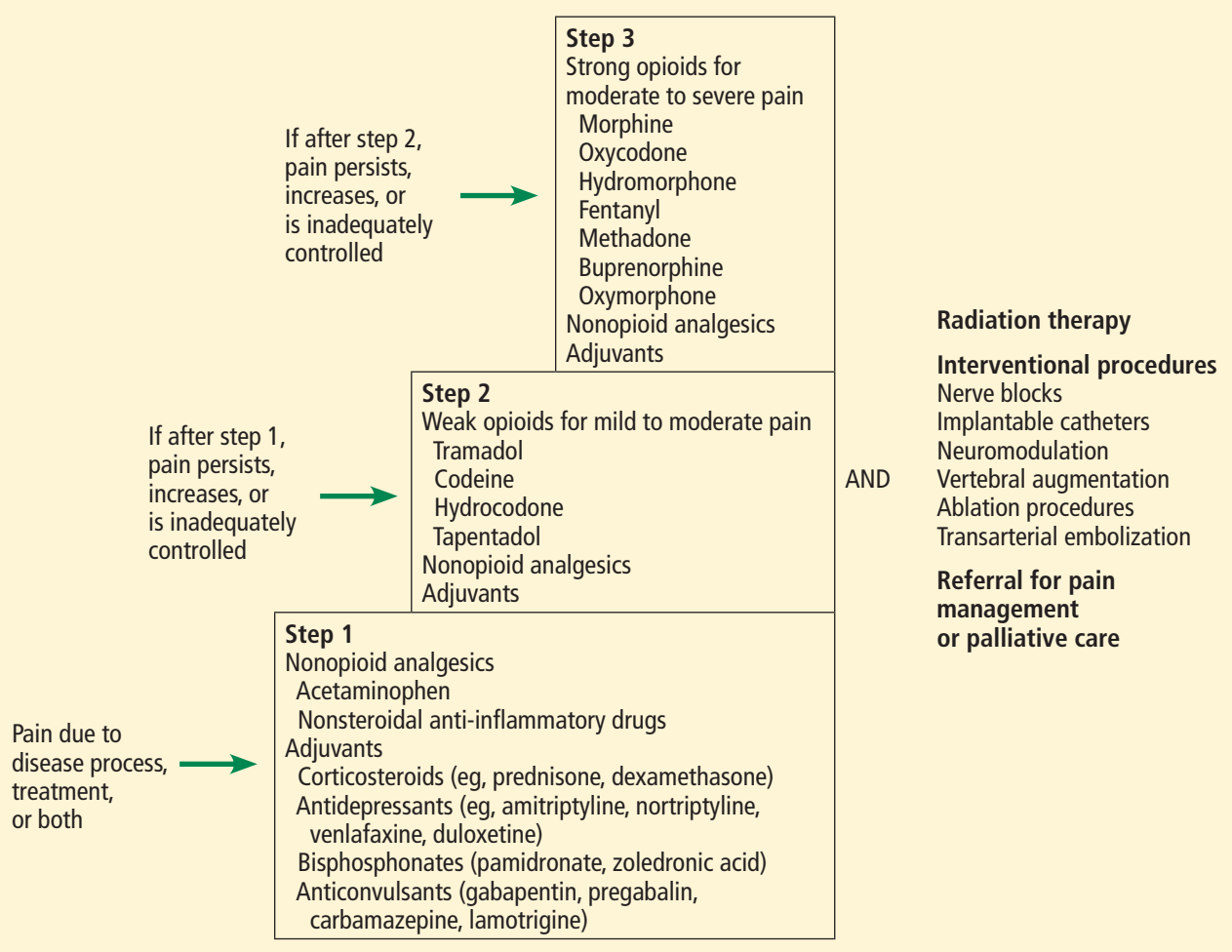

Figure 1. Our approach to managing cancer pain, based on the World Health Organization analgesic ladder.

other, nonpharmacologic interventions available for patients with cancer. It also examines pain management in cancer survivors.

WHAT ARE THE KEY PRINCIPLES IN MANAGING CANCER PAIN?

Cancer pain management often involves both drugs and procedures (**Figure 1**). The most commonly used framework that clinicians can employ in deciding which analgesic drugs to use is the World Health Organization (WHO) analgesic ladder.[2,3]

At the base, or step 1, of the 3-step ladder are nonopioid analgesics (eg, acetaminophen, nonsteroidal anti-inflammatory drugs) and adjuvants, which are used for mild pain. Adjuvants are drugs that are primarily indicated for conditions other than pain but that possess analgesic properties; they include corticosteroids (eg, prednisone, dexamethasone), antidepressants (eg, amitriptyline, nortriptyline, venlafaxine), bisphosphonates (eg, pamidronate, zoledronic acid), and anticonvulsants (eg, gabapentin, pregabalin, carbamazepine, lamotrigine).

If pain persists or increases, weak opioids for mild to moderate pain (eg, tramadol, codeine, hydrocodone) are added in step 2. If pain remains uncontrolled, strong opioids for moderate to severe pain (eg, morphine, oxycodone, hydromorphone, fentanyl, methadone, buprenorphine) are used in step 3.

At any stage, when cancer pain persists, escalates, or remains inadequately controlled, clinicians should consider specific nonpharmacologic interventions, which will be discussed below. Providers of ancillary services—nursing, social work, physical and occupational therapy,

spiritual care—may need to be called in. Similarly, specialists from fields such as radiation oncology, palliative medicine, pain management, anesthesiology, interventional radiology, surgery, and orthopedics may be essential in optimizing pain control. We recommend collaborating with specialists in either palliative medicine or pain management when step 1 of the WHO analgesic ladder fails to provide ample relief, especially for providers who are uncomfortable prescribing opioids.

WHAT ARE SOME OF THE NONOPIOID MEDICATIONS USED FOR CANCER PAIN?

Duloxetine, an antidepressant

Duloxetine, a serotonin-norepinephrine reuptake inhibitor, is primarily used to treat depression and anxiety, but it is increasingly finding a place in the treatment of diabetic neuropathy, fibromyalgia, chronic back pain, and osteoarthritic pain.[4–6] Recent studies suggest that duloxetine, alone or in combination with opioids and gabapentinoids (eg, gabapentin, pregabalin), also offers benefit in 2 cancer-related pain conditions, chemotherapy-induced peripheral neuropathy and cancer-related neuropathic pain.[7,8]

The dosing used in studies ranged from 20 to 60 mg per day. Common adverse effects are nausea, fatigue, and both insomnia and somnolence.

Cannabinoids are not recommended

The 2 most prominent and abundant cannabinoids—compounds derived from the *Cannabis sativa* plant—are tetrahydrocannabinol (THC) and cannabidiol (CBD). Preparations of cannabinoids that patients can access generally come in 3 forms:

- THC-dominant, eg, oral dronabinol and nabilone
- Balanced THC-CBD, such as oromucosal nabiximols
- CBD-dominant, such as oral CBD oil solution.[9]

Medical cannabis or marijuana preparations of all of these 3 forms are available and can be taken by various routes, such as by mouth, inhaled, or topical application.

Cannabinoids have been studied for the treatment of several cancer symptoms, notably pain, anorexia, nausea, and dysgeusia. Five randomized controlled trials from 2012 to 2018 were part of a systematic review of cannabis-based medicines for cancer pain published in 2019.[10] The review concluded that neither balanced THC-CBD nor THC-dominant preparations differ from placebo in reducing pain. Adverse effects of cannabinoids noted in studies include dizziness, dry mouth, nausea and vomiting, somnolence, confusion, and memory impairment.[9,10] Of note, nabiximols, the cannabinoid most studied for treating cancer pain, is not currently available in the United States.

The lack of quality evidence, access issues, and worrisome side effects preclude the use of cannabinoids for cancer pain at this time.

Acetaminophen

Acetaminophen (also called paracetamol) is a nonopioid medication used in step 1 of the WHO approach to managing cancer pain. Widely available in various formulations and brands, it is a popular analgesic, formulated by itself or combined with other drugs.

With regard to cancer pain, a Cochrane systematic review in 2017 concluded that adding acetaminophen to a daily regimen of 60 mg or more of oral morphine results in no additional benefit in terms of pain relief, quality of life, or patient satisfaction or preference.[11] The review was based on 3 randomized, placebo-controlled trials with 122 participants, in which the daily acetaminophen dose ranged from 3,000 mg to 4,000 mg.[12–14] The reviewers also noted that they could find no study that used acetaminophen alone for cancer pain.

Based on these findings, acetaminophen may not be of benefit when used in step 3 of the WHO analgesic ladder.

WHAT ARE SOME OF THE NEW OPIOID MEDICATIONS FOR CANCER PAIN?

Tapentadol, a mu agonist and norepinephrine reuptake inhibitor

Tapentadol has a unique synergistic mechanism of action, functioning as both a weak mu-opioid agonist and a norepinephrine reuptake inhibitor, making it the first in a new drug class.[15–17] While tapentadol has 50 times less affinity for the mu-opioid receptor and relatively moderate norepinephrine reuptake inhibitor activity, the synergy of these mechanisms generates a degree of potency comparable to that of morphine.[17]

Adjuvants are drugs that are primarily indicated for conditions other than pain but possess analgesic properties

This unique mechanism results in potential benefits. The drug causes fewer adverse effects than other opioids, especially gastrointestinal problems such as nausea, vomiting, and constipation. The time to development of tolerance is longer than with morphine, and the likelihood of abuse may be lower.[15,16] Tapentadol can also be helpful in treating neuropathic pain, with a similar mechanism as tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors.

Tapentadol is available in both immediate- and extended-release forms. There is currently no generic version available in the United States, and the drug may be prohibitively expensive or require prior insurance authorization.

Oxymorphone, a semisynthetic mu agonist

Oxymorphone is a semisynthetic mu-opioid agonist that is about twice as strong as oxycodone and 3 times as strong as oral morphine in relieving pain.[18] It has been shown to be clinically comparable to oxycodone, and it caused less respiratory depression in 1 study.[18] It is available in both immediate- and extended-release formulations.

The drug is predominantly metabolized in the liver, and, therefore, its use is relatively contraindicated in patients who have moderate to severe liver failure.[15] Its elimination in renal failure is prolonged; hence, a longer dosing interval is recommended.

Lack of evidence, access issues, and side effects preclude the use of cannabinoids for cancer pain at this time

Oxymorphone has been shown to be effective and well tolerated for managing cancer pain,[19,20] and can be considered for patients for whom other strong opioids such as morphine, oxycodone, and fentanyl have failed or who could not tolerate these drugs. Of note, oxymorphone, either in immediate- or extended-release form, generally costs more in the United States than morphine or oxycodone.

New fentanyl formulations

While intravenous and transdermal fentanyl preparations are used fairly often, a number of newer formulations are available. Transmucosal fentanyl products have been available in the form of buccal tablets, films, and intranasal sprays for a number of years, but are restricted in their use to opioid-tolerant patients (ie, those taking daily doses of at least 60 mg oral morphine or its equivalent for at least 1 week),[21] and are relatively expensive, limiting their use.

The advantages of these forms of fentanyl are rapid onset (within 10–15 minutes) and short duration of action, making them particularly beneficial in treating episodes of unpredictable breakthrough pain.[21,22] Available dosages, however, do not correspond with those of other opioids, and even doses of different fentanyl formulations given by the same route are not equivalent. Each preparation must be started at the lowest available dose and titrated up to effect when starting or changing formulations.

WHAT IS THE ROLE OF RADIATION THERAPY IN MANAGING CANCER PAIN?

Radiation therapy, or radiotherapy, has various roles in treating cancer; it is given with intent to cure the disease, arrest tumor growth, or control symptoms. As a nonpharmacologic analgesic, it is effective and time-efficient.[23] In particular, it should be strongly considered for patients suffering from painful bone metastases.

Radiation therapy generally is of 2 types, external beam and stereotactic. External beam radiation therapy, the conventional type, uses a fixed source of radiation directed toward cancerous tissue in the body. Stereotactic therapy, on the other hand, uses a moving source that targets the tumor from different angles, thereby limiting damage to nearby normal tissue. This type is typically selected for small or medium-sized tumors.

In either type, treatment can be delivered in single or multiple doses or fractions. A single fraction has been shown to be as efficacious as multiple fractions for alleviating pain from bone metastases.[24] Of note, more patients who undergo single-fraction therapy subsequently need repeat radiation therapy to the same site compared with those who receive multiple fractions up front.[25] Single-fraction therapy has the advantage of being cost-effective and convenient, especially for patients with limited life expectancy.

Of note, a transient "pain flare" can occur with radiotherapy. In a study of patients who underwent single- or multiple-fraction radiation therapy for symptomatic bone metastases, the overall incidence of pain flare within 10 days of completion was 40%.[26] The corticosteroid dexamethasone, given immediately

TABLE 1

Interventional procedures for cancer pain management

Type of intervention or procedure	Primary tumor or metastatic site indications
Nerve blocks	
Peripheral nerves	
Paravertebral	Chest-wall pain after mastectomy
Interscalene	Upper-extremity pain after surgical repair of pathologic fractures and neuropathy from brachial plexoplathy
Plexus nerves	
Celiac	Right-upper-quadrant and epigastric pain from pancreaticobiliary malignancies
Superior hypogastric	Pelvic pain from gynecologic and urologic malignancies
Ganglion impar	Perineal and rectal pain from anorectal and vulvar malignancies
Implantable catheters and neuromodulation	
Intraspinal drug delivery Spinal cord stimulation Dorsal root ganglion stimulation	Visceral pain from abdominal malignancies, neuropathic pain for lower extremities, and intractable back pain from metastases
Vertebral augmentation	
Vertebroplasty Kyphoplasty	Back pain from spine metastases and vertebral fractures
Ablation procedures	
Radiofrequency ablation Cryoablation Microwave ablation Magnetic resonance imaging-guided focused-ultrasound surgery	Pain from metastatic bone and soft-tissues sites
Transarterial embolization	Pain from hypervascular bone metastases

In survivors, opioids need to be used carefully, with the eventual goal of weaning

before single-fraction therapy and daily for 4 days after, has proven to mitigate pain flares.[27]

WHAT INTERVENTIONAL PROCEDURES ARE AVAILABLE FOR CANCER PAIN?

Some patients with cancer experience refractory pain, defined as failure of conventional oral pharmacologic agents and tumor-directed radiation therapy to control pain or such treatment causing intolerable side effects. In this situation, interventional treatments should be considered (**Table 1**). However, evidence of efficacy is lacking. Most data on outcomes are based on case reports and case series, given challenges in methodology such as accrual of adequate sample sizes for test populations and control groups.[28]

Nerve blocks

Cancer pain can affect nearly any anatomic site and may need local control using nerve or neurolytic blocks, which can be achieved by chemicals (phenol or ethanol), radiofrequency (thermal) ablation, or surgery. Nerve blocks can be performed in a peripheral nerve, plexus nerve, or central neuraxial site. In theory, any peripheral nerve can be blocked, but technical difficulties (eg, scar tissue, swelling) may preclude the procedure, and outcomes cannot

be predicted due to a dearth of evidence.[29] Examples of localized nerve blocks include paravertebral blocks for patients undergoing breast surgery[30] and interscalene blocks for surgical repair of pathologic fractures.[31]

Celiac plexus blocks are often used and are well studied in treating abdominal pain from pancreaticobiliary cancers. They have been shown to lower pain scores and decrease opioid use.[32–35] Ultrasonography-guided endoscopic celiac plexus blocks have also been performed. Though mostly based on case reports and low-quality studies with small sample sizes, positive outcomes have been described.[36,37]

Blocks to the superior hypogastric plexus for pelvic pain from gynecologic and urologic malignancies and to the ganglion impar (ganglion of Walther) for perineal pain secondary to anorectal tumors have been shown to resolve pain.[38,39] Injection can be done into the intrathecal space to achieve segmental pain control without affecting motor function.[40]

Implantable catheters and neuromodulation

For intractable tumor-related abdominal pain, neuropathic pain in extremities, or somatic low-back pain, another method of achieving central neuraxial analgesia is to use a percutaneous or implanted catheter to deliver opioids, local anesthetics, and adjuvant analgesics into the epidural or intrathecal space.[28] The dose is smaller than a systemic dose, and this route would likely benefit an individual having severe adverse effects from systemic opioid therapy.[41,42]

Managing cancer pain across its disease trajectory is complex

A randomized controlled trial in 202 patients with advanced cancer compared medical management alone vs intrathecal delivery plus medical management. The latter was associated with lower pain scores, fewer side effects, and increased survival.[43,44]

Neuromodulation is the delivery of electricity to peripheral nerves, spinal cord, and brain. Spinal cord stimulation is commonly used to treat neuropathic pain from failed back syndromes, ischemic limbs, and complex regional pain syndromes, even though there is a paucity of evidence.[45] It has been applied to cancer pain and shown to decrease pain scores and opioid use, based on case reports.[46–48] Reports of dorsal root ganglion stimulation may help pain from surgery, complex regional pain syndrome and phantom pain, and may be considered for refractory neuropathic cancer pain.[49]

Vertebral augmentation

Vertebral augmentation involves injecting polymethyl methacrylate, a cement, directly into the vertebral body (vertebroplasty) or through a balloon (kyphoplasty). Patients with vertebral compression fractures from spinal metastases may benefit from either procedure.

Kyphoplasty was shown to improve pain scores, decrease opioid use, and improve quality of life compared with medical management alone in a randomized controlled trial in 134 patients with cancer.[50] Several studies showed improved pain scores and physical function after this procedure in patients with painful, cancer-related vertebral fractures.[51–53]

Ablation procedures

Imaging-guided tumor ablation involves destruction of bone or soft tissue using radiofrequency energy, cold (cryoablation), microwave energy, or magnetic resonance imaging-guided focused ultrasound.

Radiofrequency ablation has been the most used. Patients experienced reduced pain scores and improved mood after the procedure.[54–56] Combined radiofrequency ablation and cementoplasty, in which cement is injected into bone for stabilization, have been shown to improve outcomes, as the latter provides structural stability to bone destroyed by the ablation.[57–59]

Patients treated with cryoablation experienced improved pain scores, decreased opioid use, and durable effects (ie, lasting 24 weeks or more).[60–63]

A prospective 1-year study of computed tomography-guided microwave ablation of bone metastases and soft-tissue sarcomas demonstrated a success rate (defined as ≥ 80% tumor necrosis) of 80% at 1 month and 63% at 12 months.[64] Combined with cementoplasty, microwave ablation decreased pain scores and improved ambulation in a retrospective study of 35 cancer patients with high risk of fracture.[65]

Magnetic resonance imaging-guided focused ultrasound provides more defined tumor margins for a more accurate target ablation.[66] Case series from both single centers and multiple centers showed improved pain scores and decreased opioid analgesic use.[67,68]

Transarterial embolization

Often, before orthopedic surgery, an occlusive material is injected intra-arterially to prevent perioperative bleeding from potentially bloody bone metastases.[69] This practice, called transarterial embolization, has provided pain relief for metastatic bone disease in several case series.[70–72]

HOW IS PAIN MANAGED IN CANCER SURVIVORS?

Over the years, effective treatments and innovations have yielded remarkably improved life expectancy and cure rates for patients with most types of cancer. Unfortunately, more than a third of survivors continue to suffer from cancer pain.[1]

Chronic pain in these patients can be caused by any of the 3 primary anticancer treatment approaches—chemotherapy, radiation therapy, or surgery (**Table 2**).[73,74] Many patients undergo a combination of these treatments, resulting in complex pain. Other causes of chronic pain include lymphedema, osteoporosis leading to pathologic fractures, and adjuvant drugs (eg, aromatase inhibitors, used to treat breast cancer, which cause myalgia and arthralgia).

Pain management in cancer survivors mirrors the interdisciplinary and multimodal approach for treating pain in patients undergoing active treatment. Rather than an ongoing search for a cure of the pain, preserving function and adopting coping strategies become the focus for survivors.[73]

In managing these patients, it is crucial to thoroughly assess new or worsening pain, especially when accompanied by such symptoms as unexplained weight loss, unusual fatigue, altered bladder or bowel function, persistent cough, focal numbness or weakness, or an enlarging mass.[74] This allows prompt diagnosis of cancer recurrence or progression.

The WHO pain relief ladder remains the framework for starting analgesics, with close attention to employing adjuvant medications to control neuropathic pain. Opioids need to be used carefully, and with the eventual goal of weaning. Nonpharmacologic interventions, such as nerve blocks, may be indicated for patients with refractory surgery-related pain. Patients who acquire the tendency to catastrophize or exaggerate their pain may benefit from psychosocial support provided by a social worker, psychologist, or spiritual counselor. Referral for physical therapy, occupational therapy, or both may be necessary to improve functional status in the face of chronic pain.

TABLE 2

Causes of chronic pain associated with cancer treatment

Chemotherapy
Peripheral neuropathy (with agents such as paclitaxel, docetaxel, vincristine, cisplatin, oxaliplatin, thalidomide, and bortezomib)
Osteonecrosis secondary to concurrent steroid use
Radiation therapy
Connective-tissue fibrosis
Neural damage (such as brachial plexopathy, myelopathy)
Pain from secondary malignancies
Enteritis
Proctitis
Cystitis
Vaginal dryness or atrophy
Surgery
Mastectomy (may be due to phantom breast pain, intercostobrachial neuralgia, neuroma or nerve injury)
Amputation or phantom limb pain
Thoracotomy
Head and neck surgery (eg, neck dissection)

A COMPREHENSIVE APPROACH TO A COMPLEX PROBLEM

Managing cancer pain across its disease trajectory is complex. A comprehensive, interdisciplinary, and multimodal approach combining pharmacologic and nonpharmacologic interventions provided by various disciplines and medical specialties is vital.

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