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CME MOC

Cleveland Clinic Journal of Medicine

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Hampton hump in acute pulmonary embolism

Lacrimal gland involvement in a patient with sarcoidosis

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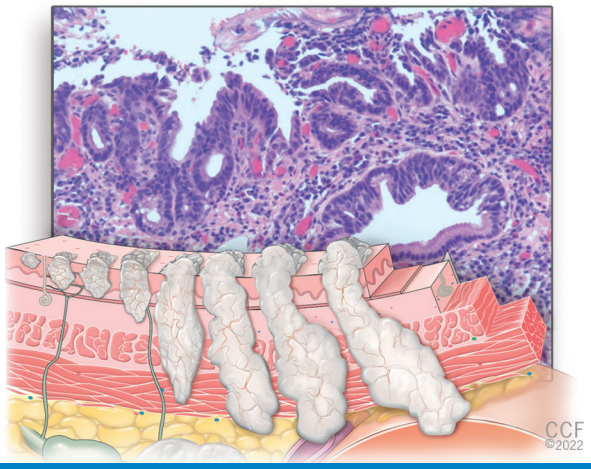

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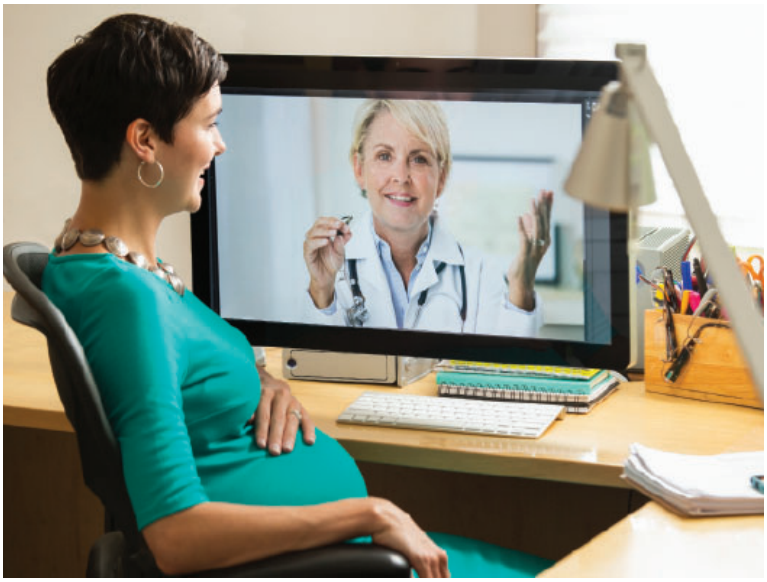

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There should be more GOLD in the EMR

The medical community approached the concept of the electronic medical record (EMR) with a mix of optimism and trepidation. Both have been realized to some extent. My workday has most certainly not been shortened, but much of my "after-hours" work can be done at home at my computer and not in the hospital reading through stacks (sometimes pounds) of paper charts containing uniquely personalized but often illegible handwritten notes. At least for patients who have received care within my own health system I can now readily access clinical notes, lab results, vital signs, and prescribed medications. This is obviously beneficial for patient care, and it facilitates efficient clinical decision-making.

Along with the mandates for utilization of electronic records and the expectation of accountability for responsible billing in clinical practice came new requirements to justify levels of billing. This quickly led to the morphing of the physician's clinical notes, initially meant for communication and archiving, into documents for billing. All-inclusive templates, drop-down menus with default responses, and parroted closing phrases stating the amount of time spent in the patient visit devoted to patient counseling and education have become the norm in both inpatient and outpatient notes. It's an amazing demonstration of physician discipline and training how that same percent of time can be provided in virtually every visit with every patient.

But the value of the clinical note as a form of communication between physicians and other caregivers has diminished significantly, with little recognition of the fact that the communication needs of different members of our "healthcare teams" are not the same.[1] In the days before cyber-medical record-keeping, I might not have been able to find or read all the physician notes, but at least I knew who wrote the note and when, and what was actually done and discussed during the patient visit. But from personal experience and what I have read in the limited literature,[2] that element of faith can no longer be taken for granted.

In addition to providing an eased shareability of information, the EMR at the least should shine in providing a platform for physicians to collect and track specific objective information necessary to implement guideline-suggested best practices. So it is disappointing to read in this issue the commentary by Ehteshami-Afshar and Merchant[3] on the lack of routine documentation in the EMR for patients with chronic obstructive pulmonary disease (COPD), especially as there is a well-accepted tool to do this that facilitates implementation of high-quality, guideline-based care, ie, the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[4]

COPD is a major cause of mortality and morbidity and repeated hospital admissions. There are many incentives for primary care and subspecialty physicians to utilize the EMR to incorporate the GOLD guidelines into routine shared patient care. But apparently, objective and subjective information is not being regularly documented and shared. Pulling objective information automatically into our notes should be a relatively simple process that can be facilitated by our information technology colleagues. But the qualitative, subjective information that impacts the interpretation of the objective air-

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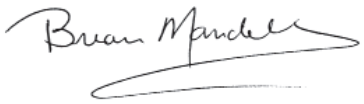
flow (and other) data must be ascertained by the clinician and then analyzed, hopefully generating a useful assessment and plan (not just an ICD code) that is transparent to the entire healthcare team.

Subjective information such as change in sputum color in the morning, vocational environmental exposures, or necessitated alteration in the path taken when walking the family's golden retriever is part of the patient's story that should overlay the interpretation of the objective information. Yet it is the patient's story, and often a detailed relevant physical examination, that is so often missing from many clinical notes. In an elegant opinion piece in *Annals of Internal Medicine*, Gantzer et al[5] presented reflections from the American College of Physicians "Restoring the Story to Health Records" task force. For those of you as frustrated as I am with the often bloated patient notes that leave me wondering how so much could be written with so little said, the Gantzer paper is a worthwhile read. I didn't get an answer to the problem by reading it, but I felt relieved that others are tackling the problem.

My clinical notes are not models for practice. But I hope that my notes are clear as to what I examined and what I asked (and forgot to ask) the patient.

Recently, I struggled with interpreting the significance of my exam finding of a left-sided systolic murmur and scant bibasilar end-inspiratory "Velcro crackles" with a single S2 and no gallop, and the patient's expressed symptom of feeling "a little" short of breath when walking up steps. This was a new patient (to me) with rheumatoid arthritis who had been treated with methotrexate and was transitioning care. A previous cardiac exam, accessible courtesy of the EMR, was described as "RRR" and the chest exam as "normal." That note included a structured list of patient responses to the review of systems, and I assume this was done to meet regulatory needs for billing, as well as to improve "personalized patient care." But none of that information was of any help to me or the patient.

As voiced by Gantzer et al,[5] practicing physicians need to retake control of the clinical note. We can do better at keeping it a useful tool for communication.



Brian F. Mandell, MD, PhD
Editor in Chief

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Hampton hump in acute pulmonary embolism

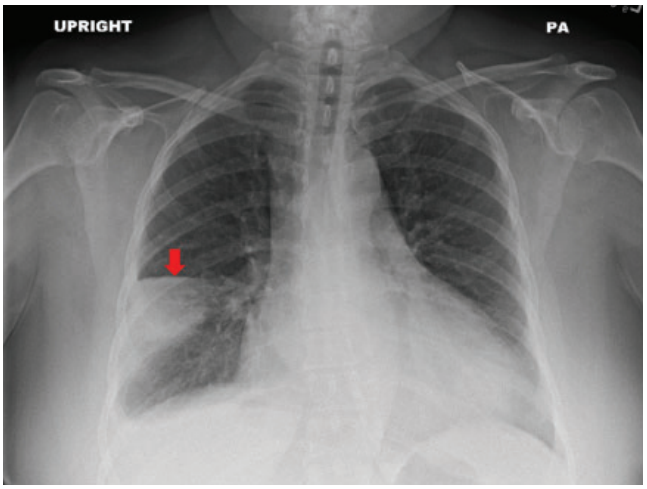

Figure 1. Posterior-anterior (PA) view of a chest radiograph demonstrated a wedge-shaped opacity (arrow) in the right middle lobe consistent with Hampton hump.

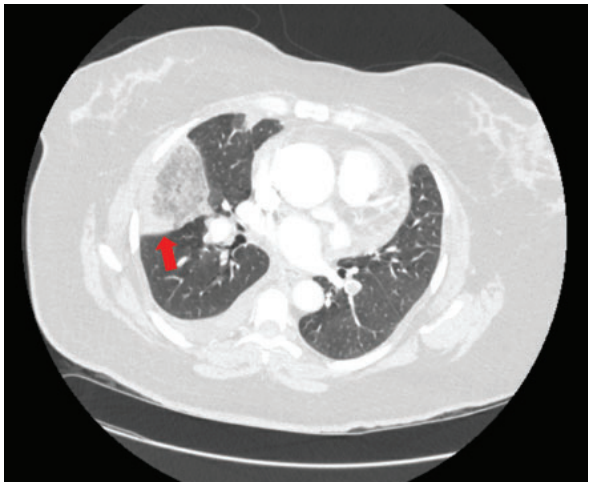

Figure 2. Contrast-enhanced axial computed tomographic angiography of the chest in a lung window demonstrated a wedge-shaped opacity (arrow) in the right middle lobe.

A 50-year-old woman with a medical history significant for childhood asthma presented to the emergency department with a 3-week history of worsening dyspnea and cough with bilateral lower-extremity swelling, left-side swelling greater than right-side swelling.

On presentation, her heart rate was 121 beats per minute, blood pressure was 197/133 mm Hg, and respiratory rate was 32 breaths per minute with oxygen saturation of 96% on room air. Physical examination was notable for tachycardia and normal S1 and S2 heart sounds without murmurs, rubs, or gallops. Breath sounds were normal bilaterally. Venous Doppler ultrasonography of the left lower extremity revealed acute distal deep vein thrombosis of the posterior tibial and peroneal veins.

Laboratory evaluation revealed the following:

White blood cell count of 13.1 × 10^9/L (reference range 3.5–10.5) with neutrophilic predominance

- Hemoglobin of 9.8 g/dL (reference range 11.5–15.5)
- Platelet count of 588 × 10^9/L (reference range 150–400)
- D-dimer of 2,669 ng/mL (reference range < 500).

Chest radiography revealed a wedge-shaped opacity in the right lower lobe (**Figure 1**) concerning for pulmonary infarc-

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tion. The patient subsequently underwent computed tomographic pulmonary angiography that revealed bilateral segmental and subsegmental filling defects consistent with acute pulmonary embolism and corresponding opacities in the right and left lower lobes consistent with pulmonary infarction (**Figure 2**). She was admitted to the hospital, and systemic anticoagulation was initiated. She ultimately did well and was discharged home. At follow-up 1 month later, her dyspnea had resolved.

HAMPTON HUMP AND PULMONARY INFARCTION

Chest radiography is the initial test of choice when evaluating patients presenting with dyspnea because it is inexpensive, widely available, and can be quickly performed at the bedside. A peripherally located wedge-shaped opacity on chest radiography is referred to as Hampton hump (**Figure 1**), first described in 1940 by Hampton and Castleman,[1,2] who performed an autopsy series to demonstrate the site of opacities seen on chest radiography in patients with pulmonary embolism compared with pulmonary infarction seen at autopsy.

Hampton hump is modestly specific for the diagnosis of pulmonary embolism but lacks sensitivity. In a study evaluating radiographs of patients in the multicenter Prospective Investigation of Pulmonary Embolism Diagnosis trial,[3] Hampton hump had a sensitivity of 22% and a specificity of 82%. Computed tomographic pulmonary angiography remains the gold-standard for establishing a diagnosis of pulmonary embolism, with a sensitivity of 89% and a specificity of 95%.[4]

Pulmonary infarction occurs when blood vessel occlusion results in mismatch of oxygen supply and demand and subsequent hypoxia. This triggers a cascade of pathologic processes culminating in tissue necrosis.[5] Pulmonary embolism is a common cause of pulmonary infarction, with an estimated annual incidence of 115 per 100,000 people in the United States.[6] The true incidence of subsequent pulmonary infarction is variable. In patients diagnosed with pulmonary embolism, pulmonary infarction has been reported in 15% to 31% of patients on follow-up autopsy and in 9% to 36% of patients on computed tomography.[5,7,8]

The lungs receive a dual supply of oxygenated blood from the bronchial and pulmonary arteries. In cases of proximal pulmonary embolism, pulmonary infarction is not typically seen owing to the presence of dual circulation.[9] However, with more distal pulmonary artery occlusions, a sudden influx of collateral blood flow into small-caliber vessels and increased vascular permeability result in intraalveolar hemorrhage and infarction.[5]

Pulmonary infarction: Presentation, risk factors, clinical significance

Clinically, pulmonary infarction can present silently or with any combination of chest pain, syncope, cough, and dyspnea. Significant risk factors include smoking, chronic obstructive pulmonary disease, malignancy, shock, and distal small-artery occlusions.[5,8] Advanced age has also historically been considered a risk factor, but recent findings suggest younger patients are at highest risk because of a less-evolved collateral system and higher endogenous nitric oxide levels that produce more vascular anastomoses and influx of bronchial flow.[10,11]

Little is known about the exact clinical significance of pulmonary infarction. According to limited data, mortality and pulmonary embolism recurrence do not significantly differ among patients with acute pulmonary embolism and ensuing pulmonary infarction compared with those without infarction.[12] Long-term consequences such as persistent dyspnea, pleuritic pain, postpulmonary embolism syndrome, and chronic thromboembolic pulmonary hypertension are not well known and should be a focal point of further investigation.

In patients presenting with dyspnea, peripheral wedge-shaped opacity on chest radiography should raise suspicion for pulmonary infarction, warranting further evaluation to diagnose pulmonary embolism. ■

The patient ultimately did well and was discharged home; at follow-up 1 month later, her dyspnea had resolved

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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Lacrimal gland involvement in a patient with sarcoidosis

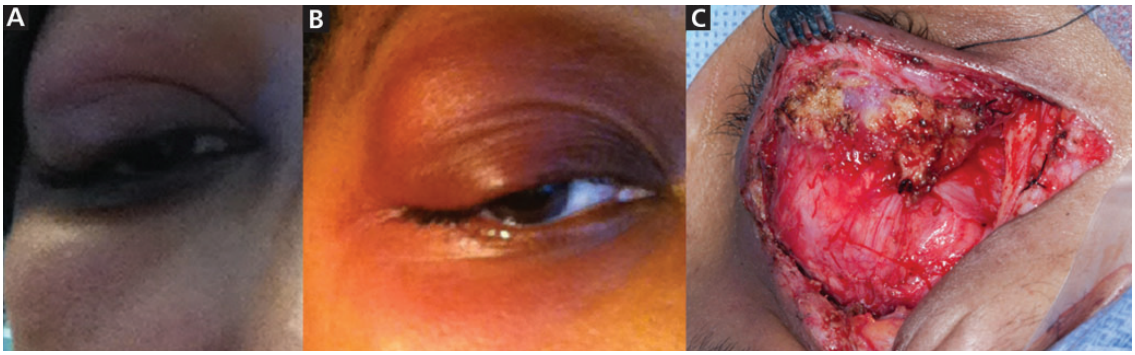

Figure 1. (A) A cellphone photo taken by the patient shows right eyelid swelling approximately 1 week after symptom onset. (B) Eyelid swelling increased, with associated ptosis and proptosis, approximately 2 weeks after symptom onset. (C) Exposure of the lacrimal gland mass during orbitotomy.

A 44-year-old woman presented to the primary care clinic with diplopia and swelling of the right eyelid that had increased over the past 2 weeks. She denied fevers, chills, headache, cough, shortness of breath, or rashes.

Physical examination confirmed right eyelid edema, with unilateral ptosis and proptosis (**Figure 1**). There was no pain with eye movements. She was prescribed doxycycline for suspected preseptal (periorbital) cellulitis. However, the eyelid swelling increased, and she was referred to an ophthalmologist for examination and imaging of the orbits.

Computed tomography (**Figure 2**) revealed abnormal soft tissue masses in the lacrimal glands of both eyes, with a larger mass in the lacrimal gland of the right eye, causing ptosis and downward displacement of the right globe. The patient underwent right anterior orbitotomy with biopsy of the right lacrimal gland. Vision and physical appearance of the left eye were not significantly affected.

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FURTHER EVALUATION PROVIDES DIAGNOSTIC CLUES

The differential diagnosis included infection, malignancy, and inflammatory disorders

The differential diagnosis for the patient's symptoms and presentation included infection, malignancy, and inflammatory disorders such as immunoglobulin G4-related disease and sarcoidosis. Biopsy of the right lacrimal gland demonstrated nonnecrotizing granulomatous inflammation, with well-formed granulomas. Histochemical staining for acid-fast bacilli and fungi was negative. There were no features concerning for malignancy. Testing for systemic inflammatory disease—computed tomography of the chest, C-reactive protein, and sedimentation rate—was nondiagnostic.

The diagnosis of sarcoidosis is based on 3 major criteria designated by the American Thoracic Society: a clinical presentation compatible with sarcoidosis (eg, lacrimal gland swelling, as in this patient), nonnecrotizing granulomatous inflammation in a tissue sample, and exclusion of other etiologies of granulomatous disease.[1] As other causes of granulomatous inflamma-

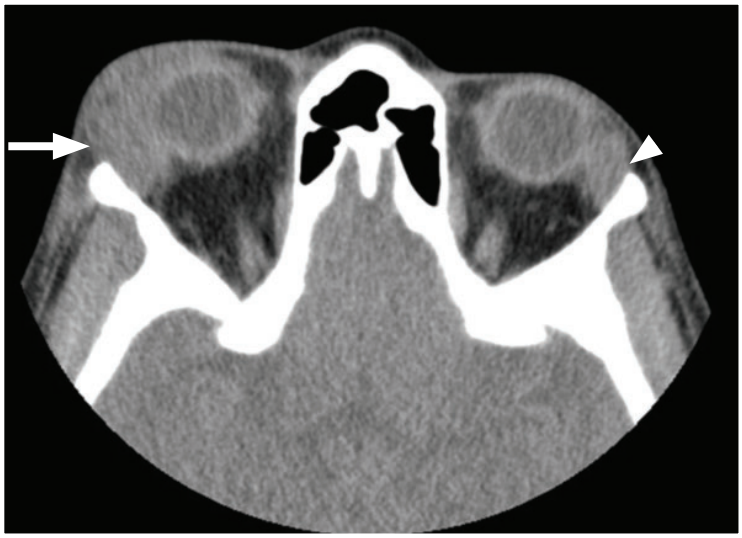

Figure 2. Axial computed tomography of the orbits showed homogeneously confluent, enlarged lacrimal glands, right (arrow) greater than left (arrowhead).

tion were felt to be less likely, sarcoidosis was favored as the cause of the patient's lacrimal enlargement. Given the absence of systemic symptoms and normal results on chest computed tomography, disease involvement was initially considered to be isolated to extraocular tissue, and the patient was diagnosed with extraocular sarcoidosis using International Workshop on Ocular Sarcoidosis criteria.[2]

ISOLATED LACRIMAL GLAND INVOLVEMENT IN SARCOIDOSIS

Sarcoidosis may affect any organ, but the lungs are usually involved. Patients frequently present with ocular involvement, which is more common in female and African American patients.[3,4]

The American Thoracic Society recommends a baseline eye examination for all patients diagnosed with systemic sarcoidosis.[1] Sarcoidosis may affect any part of the eye and its adnexa, presenting most commonly with uveitis, dry eyes, and conjunctival nodules.[3] The lacrimal gland is also often affected.[5] Significant enlargement of the lacrimal gland leads to the effects observed in our patient, ie, eyelid swelling, ptosis, and globe displacement.

Isolated lacrimal involvement is unusual. Collison et al,[6] in a small case series, concluded that although most patients with extraocular orbital sarcoidosis eventually develop systemic sarcoidosis, there are rare cases in which there is no evidence of systemic disease at the time of biopsy.[6]

Our patient eventually developed systemic sarcoidosis with biopsy-proven cutaneous lesions 10 months after the onset of extraocular symptoms.

MANAGEMENT OF OCULAR SARCOIDOSIS

Management of ocular sarcoidosis centers on initial systemic corticosteroid and immunosuppressive therapy, with or without excision.[2] Our patient's symptoms progressed on prednisone at a high dose of 80 mg and hydroxychloroquine. She has been maintained on oral methotrexate monotherapy at a weekly dose of 10 mg with folic acid supplementation.

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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A brownish erythematous patch in the nipple-areola complex

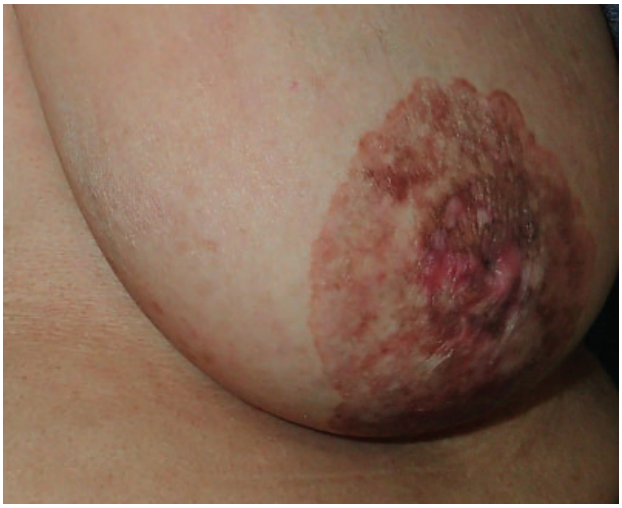

Figure 1. Brownish erythematous patch in the nipple-areola complex.

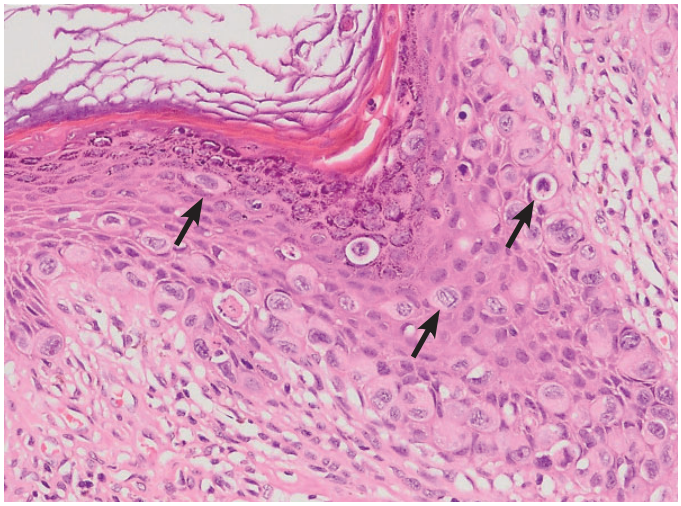

Figure 2. Skin biopsy showing single cells and small clusters of neoplastic cells (arrows) through the epidermis, with abundant pale cytoplasm (hematoxylin and eosin, × 400).

An 85-year-old woman presented with a 9-month history of pruritus in the left breast and unremarkable medical history. On examination, a brownish erythematous patch was observed in the nipple-areola complex (**Figure 1**).

Skin-punch biopsy revealed single cells and small clusters of neoplastic cells throughout the epidermis and granular layer, with abundant pale cytoplasm, intraglandular extension, and chronic inflammation in the papillary dermis (**Figure 2**), resulting in the diagnosis of Paget disease of the breast.

Mammography to rule out underlying tumor did not reveal pathologic features. Breast-conserving surgery was recommended, and the patient underwent a nipple-areola complex lumpectomy without axillary dissection, followed by adjuvant radiotherapy. Surgical specimen histologic findings were consistent with ductal carcinoma in situ of the breast, revealing sheets of neoplastic and cohesive cells in the ductal lumen. Results of immunohistochemistry showed strong staining with cytokeratin 7 (**Figure 3**) and human epidermal growth factor receptor 2 (HER-2).

Paget disease of the breast usually presents as a brownish erythematous scaly plaque affecting the nipple-areola complex.[1,2] This condition can be mistaken for other skin diseases including atopic dermatitis, allergic contact dermatitis, and Bowen disease.[3] Extramammary Paget disease, commonly located in the anogenital area or perineal area and axilla, has also been described.[1] However, while mammary Paget disease is often associated with

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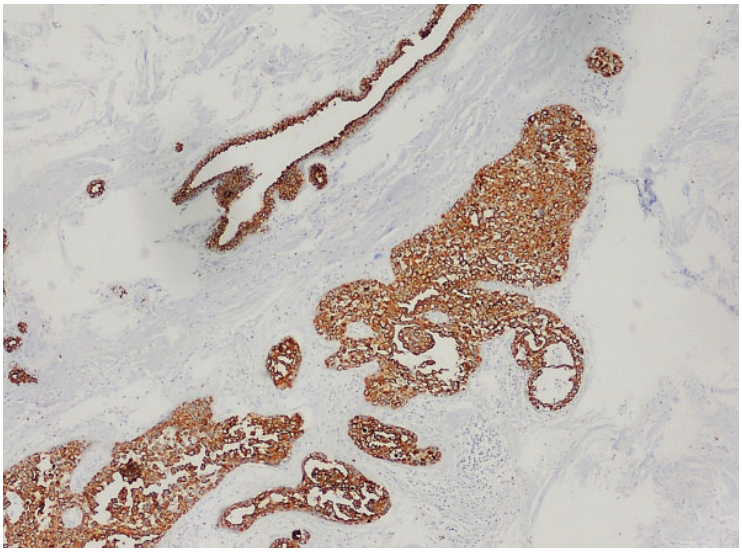

Figure 3. Strong staining of the surgical specimen with cytokeratin 7 in the surgical specimen confirmed the presence of cohesive neoplastic cells in the ductal lumen.

underlying breast carcinoma,[1–3] extramammary Paget disease with underlying malignancies occurs less frequently because Paget cells originate from ductal cancer cells that migrate from breast parenchyma along the basal membrane of the nipple.[2] These tumor cells have glandular features that are large and pale with abundant clear cytoplasms and atypical nuclei with prominent nucleoli. Expression of cytokeratin 7, GATA binding protein 3 (a regulator of mammary luminal cell differentiation), and HER-2 are useful to confirm diagnosis.[1,3]

Mammography may fail to detect neoplasms in up to 50% of patients, and disease extent can be underestimated in up to 43%.[1,4] Magnetic resonance imaging can help identify occult malignancy, axillary node involvement, and candidacy for breast conservation surgery.[1,4,5]

A high level of suspicion for nipple-areola abnormalities is required for prompt diagnosis of Paget disease. Radiologic evaluation, histopathologic study, and immunohistochemistry are essential tools in the assessment of this condition. ■

Paget disease of the breast can be mistaken for atopic dermatitis, allergic contact dermatitis, and Bowen disease

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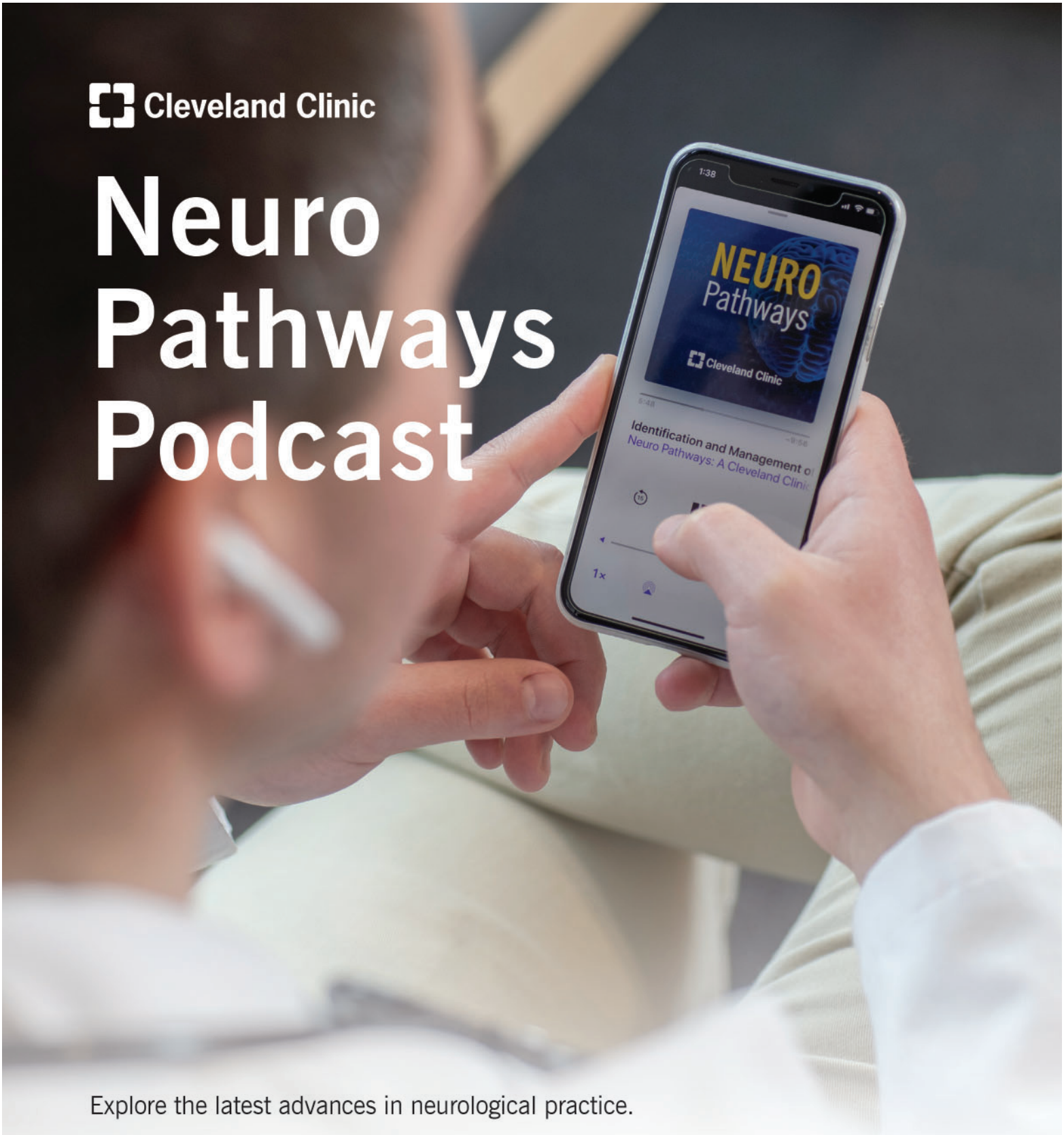

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Managing stage 1 hypertension: Consider the risks, stop the progression

ABSTRACT

The 2017 American College of Cardiology and American Heart Association Task Force on Clinical Practice Guidelines on the treatment of hypertension recommended lifestyle modification and monitoring every 3 to 6 months for patients with stage 1 hypertension. However, the guidelines did not include recommendations for patients whose blood pressure is unresponsive to lifestyle therapy. The authors review the updated AHA position statement, which is meant to help clinicians manage patients with stage 1 hypertension and a low 10-year risk of atherosclerotic cardiovascular disease.

KEY POINTS

There are no national guidelines for the treatment of stage 1 hypertension in patients with a low 10-year risk for cardiovascular disease.

This population represents an important guideline gap: most patients with stage 1 hypertension progress to stage 2 hypertension, which increases the risk for cardiovascular events.

Lifestyle modifications and, if these fail, pharmacotherapy can effectively prevent progression from stage 1 to stage 2 hypertension.

Pharmacologic therapy should be considered in patients with stage 1 hypertension who do not achieve goal blood pressure within 6 months.

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Three years after the American College of Cardiology (ACC) and American Heart Association (AHA) Task Force on Clinical Practice Guidelines published their 2017 recommendations for treatment of hypertension,[1] an important guideline gap was identified. The 2017 guidelines recommended lifestyle modification and monitoring every 3 to 6 months for patients with stage 1 hypertension, but they did not include recommendations for managing patients whose blood pressure is unresponsive to lifestyle therapy.

Patients with stage 1 hypertension have blood pressure levels of 130–139/80–89 mm Hg, have less than 10% calculated 10-year risk of atherosclerotic cardiovascular disease (ASCVD), and are unable to achieve a blood pressure goal of less than 130/80 mm Hg after 6 months of lifestyle changes. (The ASCVD Risk Estimator Plus is accessible on the ACC website.[2])

To clarify the information gap in the 2017 guidelines, the AHA released a scientific statement on the management of hypertension in this specific patient population.[3]

CLINICAL SETTING

The AHA scientific statement on the management of stage 1 hypertension in adults with a low calculated 10-year ASCVD risk focuses on outpatient management of hypertension.

INTENDED AUDIENCE

While the AHA statement is directed to practicing internists and primary care physicians, it

is pertinent to any practicing physician or advanced practitioner engaged in treating adults with hypertension or in the primary prevention of atherosclerotic events. The AHA scientific statement is relevant to all patients with stage 1 hypertension with a low 10-year ASCVD risk and assumes that no secondary causes of hypertension are involved.

WHO WROTE THE GUIDELINES?

The authors of the AHA scientific statement are nephrologists, cardiologists, internists, and a PhD epidemiologist, and the document reflects their consensus opinion. The statement is a comprehensive literature review, but its development did not utilize a more formalized method for preparation, such as the Delphi method.[4] The AHA supported the development of the scientific statement, and authors' potential conflicts of interest are listed at the conclusion of the document. Without a presumption of conflict, we note that one author received grant funding from the AHA. No other relevant conflicts of interest were disclosed.

WHAT ARE THE MAIN RECOMMENDATIONS?

The AHA statement summarizes the adverse effects of elevated blood pressure and the clinical impact of reducing it and offers lifestyle-based and medication-based treatment options. There are 5 take-home points, as follows:

- Stage 1 hypertension is prevalent in outpatient settings and usually progresses to stage 2 hypertension
- Stage 1 hypertension increases the risk for adverse cardiovascular events
- It is possible to blunt or stop the progression of stage 1 hypertension through lifestyle modifications alone
- If lifestyle modifications fail to lower blood pressure in 6 months, pharmacotherapy should be considered for patients with persistent stage 1 hypertension
- The benefits of treating stage 1 hypertension in patients with a low 10-year ASCVD risk outweigh the risks, given the elevated event rate and common progression to stage 2 hypertension.

The patient population described by the scientific statement is primarily young adults with a low incidence of cardiovascular events, reflecting the fact that age is a major risk factor for cardiovascular disease (CVD).[3,5] Randomized controlled trials powered to detect clinical events are often unfeasible in adults younger than 40 due to the large sample size and long time frame needed to detect events in a lower-risk cohort. Consequently, the AHA recommendations[3] reflect observational data on all of the following:

- The significance of hypertension on CVD risk
- Lifestyle therapy to prevent progression of hypertension
- Next steps if lifestyle therapy fails.

SIGNIFICANCE OF LIFETIME RISK FOR CVD AND PROGRESSION OF HYPERTENSION

The prevalence of hypertension increases with age, reaching 82% in US adults age 75 and older.[1,6] Up to 31.6% (95% confidence interval [CI] 27.6%–35.4%) of patients with stage 1 hypertension progress to stage 2 hypertension.[7] Before the 2017 ACC/AHA clinical practice guidelines were published, observational studies showed a proportional relationship between rising systolic blood pressure and the risk for future CVD events and all-cause mortality.[1,8–10]

There is a proportional relationship between systolic pressure and the risk of CVD events

Patients with stage 1 hypertension as defined by the 2017 ACC/AHA guidelines had an increased incidence of cardiovascular disease (hazard ratio [HR] 1.75, 95% CI 1.22–2.53) compared with their normotensive counterparts.[3,10] Another study found similar elevations in the risk for cardiovascular disease (HR 1.82, 95% CI 1.12–2.94) and stroke (HR 1.79, 95% CI 1.03–3.11) in patients with stage 1 hypertension compared to normotensive patients.[11] Recent multiple studies involving young adults stratified by the revised hypertension definitions further supported this relationship.[10–13] One study that followed Chinese participants over age 35 without CVD for 20 years found that patients with stage 1 hypertension according to the 2017 ACC/AHA guidelines had an increased risk of developing CVD (HR 1.78, 95% CI 1.50–2.11), coronary heart disease (HR 1.77, 95% CI 1.33–2.36), stroke (HR 1.79, 95% CI 1.45–2.22), and CVD mortality (HR 2.50, 95% CI 1.66–3.77) compared with normoten-

sive participants.[13] There was no relationship between stage 1 hypertension and increased CVD risk in participants over age 60.[13]

Compared with hypertension onset at a later age, hypertension in early adulthood correlates with increased carotid intima-media thickness and coronary artery calcification scores above 100 and confers a significant risk for target-organ damage and premature adverse CVD outcomes.[14,15]

BLUNTING THE PROGRESSION OF HYPERTENSION WITH LIFESTYLE THERAPY

Age-related increases in blood pressure may not be inevitable. Data suggest that low body mass index and adherence to a Dietary Approaches to Stop Hypertension (DASH) diet are associated with a low risk for hypertension over 30 years of follow-up.[1,16,17] Lifestyle modification is the cornerstone of hypertension prevention and treatment.

Lifestyle modification is the cornerstone of hypertension prevention and treatment

Although much of the data on lifestyle interventions identifies blood pressure reduction rather than clinical events as the primary end point,[1,17–21] there is a well-established relationship between rising blood pressure and adverse cardiovascular events.[11,12] Evidence-based lifestyle interventions supported by the AHA statement include reducing sodium intake, enhancing potassium intake, decreasing alcohol intake, and increasing physical activity.[1] PREMIER trial (Lifestyle Interventions for Blood Pressure Control)[21] found significant and sustained blood pressure reductions and less use of hypertensive medications (38% prevalence baseline hypertension vs 12% at 6-month follow-up, $P < .001$) in patients randomized to established lifestyle therapy (weight loss, sodium restriction, and increased physical activity) plus the DASH diet. At 18 months, there was a lower prevalence of hypertension and less use of hypertensive medications (38% prevalence baseline hypertension vs 22% at 18-month follow-up, $P > .05$).[21] The change in prevalence of hypertension between 6-month and 18-month follow-up could have derived from multiple challenges to maintain adherence to lifestyle therapy, though this was not assessed during the trial.

Blood pressure lowering associated with individual lifestyle changes tends to reduce blood pressure less than medications.[3] Because each lifestyle intervention has a modest impact on blood pressure, 2 or more interventions (eg, sodium intake and weight loss) should be targeted.[18] To promote durability in lifestyle modifications, it helps if the patient receives lifestyle counseling by a provider with expertise in behavior change.[3,22,23]

RECOMMENDATIONS WHEN LIFESTYLE THERAPY FAILS

For patients in whom lifestyle modifications do not successfully lower blood pressure below 130/80 mm Hg after 6 months, the AHA statement recommends continued lifestyle interventions and considering treatment with a thiazide diuretic, calcium channel blocker, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker. The recommendation for pharmacologic intervention applies especially to individuals with a family history of premature CVD, a history of hypertension during pregnancy, or a history of premature birth or premature menopause.[3,24–26] Several randomized trials[27–30] support the AHA emphasis on the effectiveness of pharmacologic interventions (especially with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) to prevent the progression from what is now classified as stage 1 to stage 2 hypertension.[3]

WHAT IS DIFFERENT FROM PRIOR GUIDELINES?

These recommendations for early treatment of stage 1 hypertension differ from the prior guidelines with the suggestion of pharmacologic intervention for patients whose blood pressure does not respond to lifestyle modifications. Like the 2017 ACC/AHA hypertension clinical practice guidelines, vigorous implementation of nonpharmacologic or lifestyle therapy remains the initial recommendation for patients with stage 1 hypertension who have an estimated 10-year ASCVD risk of less than 10%. The blood pressure in these patients should be reassessed after 3 to 6 months.[1]

DO OTHER SOCIETIES AGREE?

The 2018 Task Force for the management of hypertension published by the European Soci-

ety of Cardiology (ESC) and the European Society of Hypertension (ESH) recommended a systolic blood pressure goal of less than 140 mm Hg.[31] Blood pressure of 130–139/85–89 mm Hg was considered "high-normal blood pressure," and antihypertensive medications were not recommended in the absence of very high cardiovascular risk due to established CVD. However, patients with a calculated 10-year ASCVD score of 5% to 10% were considered at high risk. Further, the ESC/ESH guidelines note that antihypertensive drugs may be considered in patients with blood pressure close to the threshold of 140/90 mm Hg after a prolonged attempt to control blood pressure with lifestyle changes, and they suggest that other conditions such as a family history of premature CVD and human immunodeficiency virus infection increase cardiovascular risk.[31]

HOW WILL THIS CHANGE DAILY PRACTICE?

Patients should be informed that many patients with stage 1 hypertension can lower their blood pressure via intensive lifestyle therapy without the need for medication, but also that medication might be a reasonable option if lifestyle changes do not achieve the desired effect.[17,21] If lifestyle therapy fails to lower blood pressure to less than 130/80 mm Hg, patients and physicians should have some reassurance from trials from trials by Zhang et al[32] and by the SPRINT Research Group.[33] These trials demonstrated that targeting a systolic blood pressure goal of less than 130 mm Hg in patients with hypertension who are over age 50 resulted in lower rates of fatal and nonfatal major cardiovascular events and lower all-cause mortality without increasing the risk of adverse events from drug therapy used to achieve a lower blood pressure.[32,33]

Given the significant proportion of patients with stage 1 hypertension who progress to stage 2 hypertension and the stepwise increase in cardiovascular risk with each successive stage, we believe that the aggressive treatment of stage 1 hypertension can reduce cardiovascular events.

WHEN WOULD THE GUIDELINES NOT APPLY?

The recommendations provided in the AHA scientific statement apply only to patients in whom lifestyle therapy was not effective at reducing blood pressure to less than 130/80 mm Hg after 6 months. These guidelines do not apply to patients who achieve a blood pressure of under 130/80 mm Hg with 6 months of lifestyle therapy, who are already on antihypertensive medications, or who have secondary causes of hypertension.

THE BOTTOM LINE

The updated AHA position statement is meant to assist clinicians in navigating an important guideline gap in the 2017 ACC/AHA recommendations, ie, the management of patients with stage 1 hypertension and a low 10-year ASCVD risk. The authors of the position statement correctly claim that patients who do not achieve a blood pressure goal of less than 130/80 mm Hg after 6 months of lifestyle therapy should be considered for pharmacologic therapy. However, we believe that clinical judgment should prevail. The ACC/AHA recommendations are population-based and may not apply to individual situations. Both the AHA statement and 2017 ACC/AHA guidelines should serve as a conceptual framework for clinicians, but they do not replace patient-centered conversations between patients and providers. ■

Guidelines are valuable conceptual frameworks but do not replace patient-doctor conversations

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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COMMENTARY

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The underappreciated role of documentation in improving COPD care

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is the third leading cause of death worldwide,[1] and the third leading cause of hospital readmissions in the United States.[2] COPD continues to be a major economic burden on healthcare systems, due to the high number of hospitalizations caused by severe exacerbations.[3]

Since its first publication in 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[4] has been widely used as the de facto standard for evidence-based management of COPD. But despite the well-known importance of providing guideline-concordant care, studies have shown that there are still barriers to implementing evidence-based recommendations in providing care for patients with COPD.[5,6]

While there may be many root causes of poor uptake of COPD guidelines in clinical practice, a contributing factor not well explored is the improper documentation of the refined GOLD assessment tool and exacerbation risk to accurately identify the disease burden and plan an appropriately customized treatment plan.

In 2011, GOLD guidelines added symptom severity and exacerbation history to the classification system for COPD rather than relying solely on evidence of airflow limitation based on forced expiratory volume in 1 second on spirometry.[7] The goals of GOLD COPD assessment are to determine not only the level of airflow limitation but also its impact on the patient's health status and the risk of future events (eg, exacerbations, hospital admissions, death), in order to guide therapy to both reduce the symptom burden and improve the clinical outcome.[8] Even though airflow limitation has an important role in predicting population-level outcomes, at the individual patient level, it loses accuracy if used alone without considering the symptom burden and risk of exacerbations to guide the choice of therapy.

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ACCURATE DOCUMENTATION IS AN IMPORTANT FIRST STEP

Improper documentation of the GOLD assessment tool contributes to poor uptake of COPD guidelines

The development of guidelines is an important step in the care of patients with COPD. But to improve care, guidelines need to be adopted into practice, and accurately identifying and documenting COPD is an important first step toward guideline-based care.

Regularly, patients are classified as having COPD in clinical documentation with no additional notes to specify the COPD symptom burden or exacerbation risk assessment, as suggested by GOLD. Jouleh et al[9] showed that patients classified with a higher GOLD stage are significantly more likely to receive guideline-concordant care, and this might be due to higher referral of these patients to subspecialists to receive care. Belletti et al[10] found that in 11 primary care settings, only 48% of the 1,517 patients diagnosed with COPD had documented GOLD classifications. In 14,130 patients with COPD in a cohort of the Optimum Patient Care Research Database from the United Kingdom during 2002–2010, 16% had an unknown GOLD assessment group.[11]

Studies show missed documentation

Interestingly, not many studies have reported the rate of proper documentation of COPD assessment in their populations, possibly because patients with insufficient data to be classified into appropriate GOLD assessment groups have been excluded from the studies. This can also explain the gap in the evidence regarding this phenomenon. These findings are very similar to a study of missed documentation of chronic kidney disease in which clinicians frequently documented the disease as a general term in medical records without consistently including additional specification on the stage.[12]

POOR DOCUMENTATION HINDERS QUALITY-IMPROVEMENT PROJECTS

Many quality-improvement projects are geared toward implementing evidence-based interventions in clinical settings to improve clinicians' adherence to the published guidelines and the subsequent care for COPD patients. Insufficient and nonstandardized documentation of a comprehensive COPD assessment makes the evaluation of quality of care challenging.

Insufficient documentation of a comprehensive COPD assessment makes the evaluation of quality of care challenging

Reasons behind missed documentation of a comprehensive COPD assessment may be the pace of the ambulatory clinics, electronic medical record fatigue, lack of training on how to obtain a disease-specific COPD history, and the lack of appropriate documentation or knowledge regarding guideline recommendations. At times, dual management of COPD care by a primary care physician and a pulmonologist may contribute to incomplete or inaccurate documentation of the COPD assessment, as each clinician may defer the task of accurate documentation to the other.

Overdiagnosis and underdiagnosis of COPD

It is worth mentioning that both overdiagnosis and underdiagnosis of COPD are major obstacles to improving management of COPD. Underutilization of spirometry is the main reason, but patient-related factors such as exposure to airborne pollutants, patient age and educational level, and language barriers have been identified as potential contributors, and these in turn can affect the comprehensive initial assessment and subsequent documentation of the findings.[13–15]

GOALS FOR IMPROVING COPD DOCUMENTATION

Disseminating the results of the quality-improvement efforts among healthcare institutions is an essential step toward improving the care throughout the healthcare systems.[16,17] If the state of nonstandardized assessment of COPD disease-burden documentation does not improve, assessment of current status and data-sharing between clinicians or institutions will be inaccurate. This will have a negative impact on the quality of provided care and will reduce the pace of quality-improvement efforts in COPD care.

We urge clinicians providing care to patients with COPD to accurately assess the patient's exacerbation risk and COPD disease burden using the refined GOLD "ABCD" assessment tool,[18] which is a well-recognized, accepted, easy-to-use tool, and also to document the assessment in the patient record to allow better uptake of guideline-based care. For patients who receive dual care from a primary care physician and a pulmonologist, this can be done as a collaborative effort. We also propose that future studies on the uptake of COPD guidelines consider the importance of documenting the COPD disease-burden assessment.

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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Psychogenic nonepileptic seizure: An empathetic, practical approach

ABSTRACT

Psychogenic nonepileptic seizure (PNES) is often misdiagnosed as epilepsy, leading to unnecessary treatments and procedures, as well as failure to engage patients in needed mental health care. To establish an accurate diagnosis, video electroencephalography (EEG) in the context of and simultaneous with a comprehensive neurologic and psychosocial evaluation is recommended for any patient with seizures that are not responding to treatment. Delivering the diagnosis with empathy and respect is a crucial component of care that helps patients establish trust with caregivers and follow treatment recommendations. Effective treatment is available, highlighting the importance of early diagnosis to avoid unnecessary and potentially harmful treatment. But there are many barriers to care, including provider misperceptions, lack of acceptance of the diagnosis, poor patient engagement with treatment, and lack of access to care.

KEY POINTS

- PNES resembles epileptic seizure in signs and symptoms but is due to psychological distress, a form of conversion disorder.
- PNES is frequently misunderstood as being consciously feigned, and patients often feel accused of "faking" their seizures.
- Inpatient video EEG in an epilepsy monitoring unit is the gold standard for diagnosis.
- Psychotherapy should be tailored to the predisposing, perpetuating, and precipitating factors that contributed to the development of PNES.

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A 19-YEAR-OLD RIGHT-HANDED MAN who had meningitis at age 12 presented with seizures that had begun 12 months earlier. He described the seizures as bilateral arm-stiffening and stuttering speech, followed by rocking movements of the head and trunk that waxed and waned over 30 to 40 minutes. He said he never lost consciousness. He identified lack of sleep and stress as triggers.

The patient was brought to a local emergency department in the midst of a prolonged seizure and was treated with intravenous lorazepam. He was evaluated by a local neurologist, who prescribed levetiracetam for the seizures. Results of routine outpatient electroencephalography (EEG) and brain magnetic resonance imaging were normal. He continued to have seizures, despite escalation of levetiracetam doses.

See related article, page 260

He was admitted to the epilepsy monitoring unit for continuous video EEG monitoring. Several typical episodes were recorded and confirmed by family members and the patient. The episodes were characterized by gradual onset of irregular jerking of his head and arms, followed by arm and truncal stiffening and initial eyes-closed unresponsiveness. He then gradually started following commands but continued to have irregular bilateral jerking movements for 10 more minutes. No epileptiform EEG changes were seen before, during, or after the episodes. Likewise, interictal EEG over 72 hours was normal. He was diagnosed with psychogenic nonepileptic seizure (PNES).

PREVIOUSLY KNOWN AS PSEUDOSEIZURE

Previously known as pseudoseizure, PNES resembles epileptic seizures in symptoms and signs but is not caused by abnormal epileptiform electrical activity in the brain. Instead, this disorder is a manifestation of underlying psychological distress and unresolved emotions. Many people diagnosed with PNES meet the criteria for conversion disorder (also known as functional neurological symptom disorder) or other somatoform disorder, and others meet the criteria for dissociative disorder.

Multiple terms have been used to describe PNES, including dissociative seizure, functional seizure, stress seizure, and nonepileptic attack, reflecting the difficulty of finding a term that respectfully indicates both the psychological nature of the condition and its superficial similarity to epilepsy. The long-entrenched term pseudoseizure has been misinterpreted by patients and physicians as meaning the patient is "faking" or feigning the seizures. Unfortunately, this view has negatively influenced how some healthcare providers treat patients with PNES.

Importantly, there are other causes of nonepileptic events besides PNES—eg, syncope, migraine (which can be accompanied by transient focal neurologic symptoms and signs), paroxysmal dystonias, and other movement disorders. Rarely, a nonepileptic event is due to intentional deception as in factitious disorder or malingering. In some people with developmental or intellectual disabilities, nonepileptic events are behavioral or attention-seeking. PNES is distinctly different in that it is not conscious or intentional.

PATHOPHYSIOLOGY

The pathophysiology of PNES is unclear, but the literature suggests PNES is a network disorder affecting sensorimotor processing, emotional regulation, and neural responses to stress.[1] Functional neuroimaging studies provide some evidence that people with PNES have abnormalities in limbic brain structures including the amygdala, hippocampus, parahippocampal gyrus, insula, cingulate cortex, and prefrontal cortex.[2]

EPIDEMIOLOGY

PNES can develop at any age but is most common between ages 15 and 35.

The disorder is more common in women, and particularly in women who have been victims of abuse.[3] Childhood abuse (sexual, emotional, or physical) is strongly correlated with subsequent development of PNES.[4] Psychiatric disorders such as depression, anxiety, and posttraumatic stress disorder (PTSD) are also commonly seen in patients with PNES, as discussed further below.

Early studies estimated the prevalence of PNES at 2 to 33 per 100,000.[5] A 2021 systematic review calculated the incidence of PNES in the United States at 3.1 per 100,000 per year, and the prevalence at 108.5 per 100,000.[6] In a 2021 population-based study in Norway, the mean annual incidence of PNES was also found to be 3.1 per 100,000 per year; the prevalence was 23.8 per 100,000, with the highest prevalence among 15- to 19-year-olds at 59.5 per 100,000.[7] In comparison, epilepsy has an incidence of 62 per 100,000 per year[8] and a prevalence of 1.2%, or 1,200 per 100,000.[9]

From 25% to 35% of patients referred to epilepsy monitoring units for video EEG are diagnosed with PNES.[10,11] The disorder is often misdiagnosed as epilepsy, placing patients at risk of iatrogenic complications related to unnecessary antiseizure medications and inappropriate medical interventions such as intensive care unit admission, benzodiazepine administration, and oral intubation. In a study of 384 patients diagnosed with status epilepticus and treated unsuccessfully with benzodiazepines, 10% were ultimately determined to have PNES.[12]

The term pseudoseizure has been misinterpreted as meaning the patient is 'faking' or feigning seizures

PNES is associated with poor quality of life[13] and high rates of unemployment and disability.[14] Mortality rates are also higher in people with PNES than in the general population, with one study finding that 20% of deaths in those with PNES under age 50 were due to suicide.[15]

DIAGNOSED BY HISTORY AND VIDEO EEG

A comprehensive history and video EEG during a typical seizure are the gold standard for diagnosing PNES. There should be no epileptiform abnormalities on the EEG before, dur-

TABLE 1

Clinical features that may suggest psychogenic nonepileptic seizure[a]

Long duration (> 10 minutes) of convulsive-type seizures
Convulsive-type seizures with retained awareness
Side-to-side head movements during convulsive-type seizures
Out-of-phase limb movements
Eyes-closed unresponsiveness
Pelvic thrusting
Fluctuating patterns of movement
Distractibility during the seizure
Crying during the seizure
Stuttering during the seizure

[a] No one sign is 100% specific for psychogenic nonepileptic seizure. History alone is not a substitute for confirmation with video electroencephalography.

ing, or after a typical event.

Absence of EEG changes alone, however, is not always diagnostic. EEG must be interpreted in the context of clinical signs and symptoms. Features of seizure semiology or symptomatology that are highly predictive of PNES include long duration of convulsive-type seizures (> 10 minutes), convulsive-type seizures with retained awareness, rapid side-to-side head movements, out-of-phase limb movements, eyes-closed unresponsiveness, and pelvic thrusting (**Table 1**).[16] Fluctuating patterns of movement and distractibility during the seizure are also suggestive of PNES.

Many patients with PNES say the diagnosis is confusing and distressing, and they feel misunderstood, mistreated, and blamed

No one sign is 100% specific for PNES. For instance, out-of-phase limb movements and pelvic thrusting can occur in frontal lobe epileptic seizures, without a clear ictal EEG change.

Video EEG is most helpful when there are motor signs or decreased responsiveness, but like most diagnostic tools, video EEG has limitations. For instance, if the onset of the seizure is not captured on video, postictal behavior can be confused with PNES.

Importantly, video EEG is less useful when the patient has only subjective symptoms, because epileptic aura (with purely subjective symptoms) can be scalp EEG-negative. In addition, certain epileptic seizures can be scalp EEG-negative due to movement artifact or because scalp EEG has difficulty recording from deeper areas of the brain. In these cases, referral to a comprehensive epilepsy center is recommended. As mentioned earlier, other nonepileptic events to consider are migraine, vertigo, syncope, movement disorder (eg, paroxysmal dystonia and dyskinesia), and sleep disorders such as narcolepsy, cataplexy, and parasomnias.

About 10% of patients with PNES also have epileptic seizures, so when the patient or the patient's family describes more than 1 seizure type, it is crucial to record examples of all seizure types. Once it is confirmed that a patient has both PNES and epileptic seizures, showing the patient and family videos of the seizure types captured with video EEG, and highlighting key features of both seizure types, will help them distinguish PNES from epileptic seizures once they leave the monitoring unit.

COMMUNICATE THE DIAGNOSIS CLEARLY AND WITH EMPATHY

Presenting the diagnosis to the patient is typically the job of the neurologist who has interpreted the video EEG. Communicating the diagnosis effectively is crucial and can be therapeutic in the short term. However, if learning the diagnosis leaves the patient angry or confused, PNES and other psychiatric symptoms will likely worsen.

A survey of primary care and emergency medicine physicians found that 38% believed that episodes of PNES are intentionally produced or faked, and 63% did not feel video EEG was needed to confirm a diagnosis of PNES.[17] The misperception that PNES is intentionally feigned is likely to result in mismanagement of the condition.

Many patients with PNES say the diagnosis is confusing and distressing, and they feel misunderstood, mistreated, and blamed when they seek medical care.[18] About a quarter feel the diagnosing doctor does not understand their PNES symptoms.[19] Receiving a diagnosis of PNES can be particularly confusing for patients who were previously diagnosed with epilepsy and treated for years with anti-

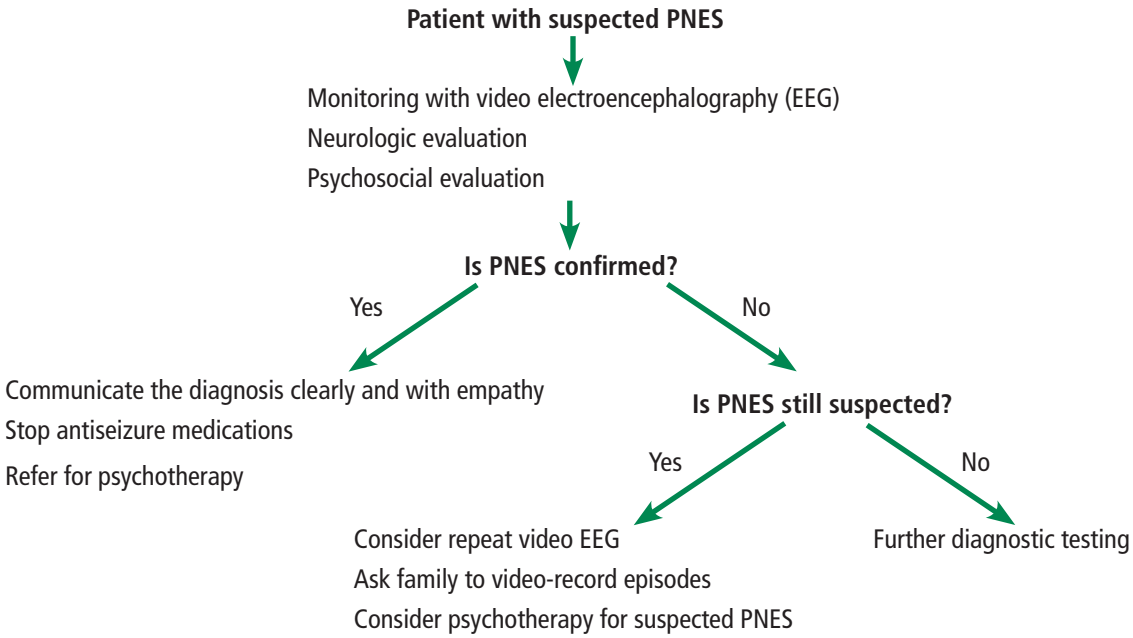

Figure 1. Algorithm for diagnosing psychogenic nonepileptic seizure (PNES).

seizure medications.[20] When their diagnosis is changed from epilepsy to PNES, patients find the news distressing because they perceive the burden of recovery is shifted from the doctor's shoulders to theirs.[21] Misperceptions about PNES and poor physician-patient communication certainly add to the emotional struggles of patients and can lead to resistance to mental health recommendations.

Since many people with PNES have a history of trauma and abuse, perceived or actual mistreatment by medical providers (via poor communication of the diagnosis) can traumatize them yet again and makes it more likely they will reject the diagnosis. Various communication strategies have been proposed, but the most important component is to deliver the diagnosis with empathy and clarity.

Key points in discussing the diagnosis with the patient are to acknowledge that their symptoms are real and can be frightening and disabling. It can be reassuring to know that they are not alone and that PNES is a diagnosis that is common in epilepsy monitoring units.

The discussion should also clarify that the patient does not have epilepsy and does not need antiseizure medications (assuming the patient does not have comorbid epileptic seizures). Rapid titration off antiseizure medications at the time of diagnosis is associated with better outcome than with delayed titration.[22]

It is helpful to discuss the role of emotions and stress in producing physical symptoms, similar to the way anxiety can cause abdominal pain or headaches. Finally, it is essential to let the patient know that with treatment PNES can resolve, and that seizure control with a return to normal function should be the goal. These steps are summarized in **Figure 1**.

Key points when discussing the diagnosis with the patient are to acknowledge that their symptoms are real and can be frightening and disabling

TREATMENT

Emergency management

The basics of emergency medical care apply in people having a known or suspected PNES episode, as follows:

- Monitor airways, breathing, and circulation
- Provide for patient safety and comfort
- Avoid employing noxious stimuli (eg, sternal rub) in an attempt to test responsiveness
- Remain calm and reassuring
- Stay with the patient until symptoms start to improve.

If the PNES diagnosis is clear from a previous video EEG evaluation and if the situation allows, encouraging the patient to engage in deep breathing can help to lessen the intensity of the episode. Once the episode has resolved,

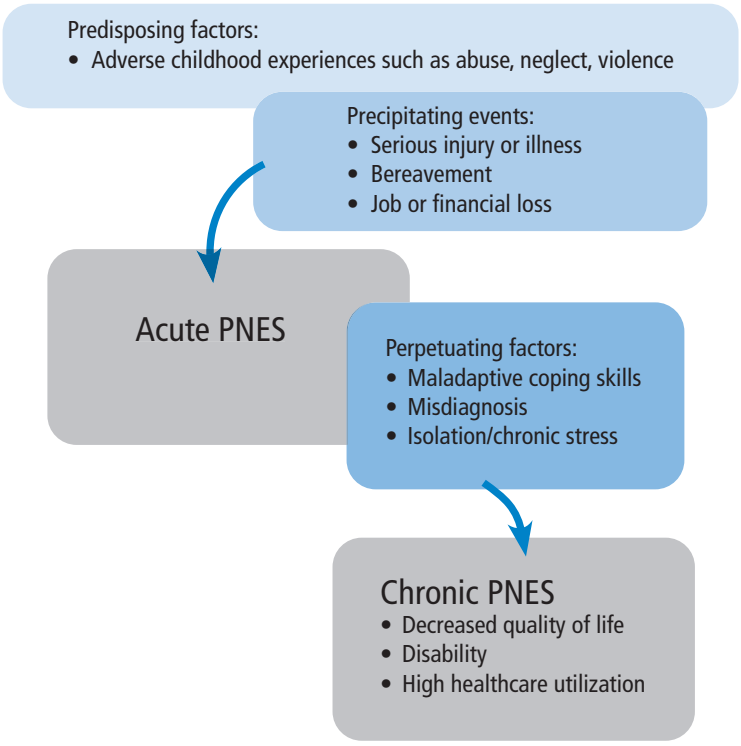

Figure 2. A variety of predisposing, precipitating, and perpetuating factors contribute to psychogenic nonepileptic seizure (PNES). Patients with PNES typically have multiple contributing factors.

prompting the patient to identify potential triggers for the episode can be instructive and ultimately empowering.

If the seizure diagnosis is not clear, PNES should still be considered, if only briefly, before initiating escalating doses of antiseizure medications in an emergency setting.

Predisposing, precipitating, and perpetuating factors

Biologic, psychological, and social factors all contribute in a complex way to predisposing patients to PNES, precipitating episodes, and perpetuating the condition, thus making it chronic (**Figure 2**).

Biologic factors include a history of head injury and of somatic conditions such as migraine, asthma, irritable bowel syndrome, chronic pain, and insomnia.

Psychological factors associated with PNES include mood disorder, anxiety, PTSD, and maladaptive coping styles. Exposure to trauma early in life can contribute to the emergence of psychiatric symptoms such as somatic dissociation due to inability to regulate emotions and cope with distress. Maladaptive coping styles, particularly the avoidant coping style and alexithymia (inability to identify and describe emotions), can make people susceptible to develop somatic symptoms as a means to release tension. Heightened somatic hypervigilance, excessive symptom preoccupation, and learned somatization can all contribute to the development of PNES.[23,24]

Social factors include a history of abuse, chronic stress, drug use, family dysfunction, marital discord, and financial instability.

A single factor can play multiple roles, both predisposing to and perpetuating PNES. Typically, a combination of biopsychosocial factors including physiological susceptibility, early-life trauma, maladaptive response to psychological distress, and ongoing social stressors can lead to the development and chronicity of PNES.[25]

Psychiatric disorders: Cause or comorbidity?

Symptoms of PNES are considered maladaptive defense mechanisms that develop in response to an underlying psychiatric disorder.[26] Therefore, coexistent psychiatric disorders can be understood as causes of PNES rather than comorbidities. This relationship can be bidirectional, with psychiatric symptoms contributing to the emergence of PNES, and the struggle with PNES exacerbating existing psychiatric disorders. Therefore, the assessment and treatment of PNES should include identifying and addressing coexisting psychiatric disorders along with the PNES symptoms.

Common psychiatric comorbidities in patients with PNES include the following[27]:

- PTSD (35%–49%)
- Depressive disorders (57%–85%)
- Dissociation (22%–91%)
- Other somatoform disorders (22%–84%)
- Axis II (personality) disorders (10%–86%).

Suicidal ideation is common in individuals with PNES, with 39% acknowledging suicidal ideation and 20% reporting suicide attempts in 1 study.[28] Panic attacks, history of trauma, and history of sexual and physical abuse are also highly prevalent.

The high prevalence of trauma exposure and psychiatric comorbidity reflects the ex-

treme vulnerability and psychological distress that patients with PNES suffer and helps explain the critical need for psychological support. A misperception of the condition as consciously feigned slights the patient's struggle, increases distress, and worsens PNES symptoms.

Psychotherapy is effective

PNES is treatable, as demonstrated by 2 pilot randomized controlled trials of 12-session courses of cognitive behavioral therapy (CBT).[29,30] A meta-analysis of psychological interventions including CBT found that 47% of patients with PNES became seizure-free, and 82% showed a reduction in seizures of at least 50%.[31] PNES-tailored counseling interventions, particularly CBT-based, also improve health-related quality of life and psychosocial functioning.[32]

PNES-specific counseling interventions often include education about types of seizures, identifying and managing common seizure triggers, aura interruption methods, and improved emotion management skills using relaxation training and other CBT techniques.[29]

As mentioned earlier, controlling underlying psychiatric symptoms is an important part of treating PNES. In the case of ongoing psychiatric symptoms such as PTSD, various evidence-based psychotherapy interventions can be used concurrently or subsequently, including the following:

- Hypnosis
- Eye movement desensitization and reprocessing
- Prolonged exposure therapy for patients with coexisting PTSD symptoms[33]
- Cognitive processing therapy
- Intensive outpatient programs for mood disorders
- Dialectical behavioral therapy for patients with severe personality disorders[34]
- Family therapy, often incorporated in individual counseling because of the high prevalence of family dynamic stress in patients with PNES.[35]

Pharmacologic therapy for some

Although counseling is the best intervention, antidepressants are often used to treat PNES, particularly in patients with low psychological insight or poor engagement with counseling for other reasons.[29–32] There is some evidence that antidepressants alone,[36] as well as antidepressants with counseling,[29] can result in reduction of PNES episodes.

The benefit from benzodiazepines is mixed. Although some patients may benefit from benzodiazepines for anxiety, clobazam and clonazepam have been associated with behavioral side effects that can mimic PNES.[37]

Stop antiseizure medications

Continuing antiseizure medications in patients with PNES has been associated with poor outcome.[38] When the diagnosis of PNES is clear, antiseizure medications should be stopped unless they are being used to manage comorbid epilepsy, chronic pain, migraine, or mood instability.

IMPROVING TREATMENT ADHERENCE

Effective treatments are available for PNES, but challenges remain, especially lack of access to treatment and patient rejection of both the diagnosis and treatment.

High attrition and poor treatment engagement are known challenges in the treatment of PNES. Predictors of poor treatment adherence include insufficient understanding of the diagnosis, unemployment, and severe psychiatric and personality disorders.[28,39] Communicating the diagnosis without sufficient explanation or a clear treatment path rarely produces a good outcome, whereas patients who are given sufficient time and education about the diagnosis, as well as psychiatric support, show better outcomes.[40,41]

Effective treatments are available for individuals with PNES

Although physicians have no control over the patient factors that predict poor treatment engagement, they do have control over how they explain the diagnosis, which in turn can affect the patient's acceptance of the diagnosis, which is the first step in treatment engagement. Introducing the diagnosis may initially invoke intense emotions in patients, but taking sufficient time to explain PNES and answer questions, using an empathic approach to validate patients' reactions, can help ease patient distress. Recognizing that shame and embarrassment are common reactions in these situations, a dignified and respectful conversation during the delivery of the

PNES diagnosis can help the patient to be receptive of the physician's recommendations.

The psychological approach known as motivational interviewing, often used to engage treatment-resistant patients, was shown in a randomized control trial to improve patients' acceptance of the diagnosis, adherence to treatment, and quality of life, as well as to reduce the frequency of PNES episodes.[42] Empathic and clear communication of the diagnosis and allowing sufficient time to address all of the patient's concerns and questions are critical components of the treatment of PNES.

MORE ABOUT OUR PATIENT

We talked to the patient further and found that he began to have depressive symptoms after his grandmother died, 4 years before the onset of his seizures. In the year after her death, he began to drink alcohol and abuse drugs.

After graduating from high school in May 2020, he joined the military, but soon after, he tested positive for COVID-19 and was placed in quarantine. Being diagnosed with COVID-19 early in the pandemic when there was so little information available was a traumatic experience for him. He felt helpless and had severe crying spells because he thought he was going to die. His quarantine "buddies" were likewise experiencing depressive symptoms, and he witnessed multiple episodes of self-injurious behavior among the other recruits. While in quarantine, he developed seizures and was hospitalized.

He was eventually discharged from the military and returned home. He then enrolled in college, where he struggled with his classes and had a series of failed romantic relationships.

In the epilepsy monitoring unit, he was diagnosed with anxiety in addition to PNES. The diagnosis of PNES was explained in the context of his recent stressors, and though he was tearful, he said he felt relieved to know he did not have epilepsy. He and his family understood and accepted the PNES diagnosis, and outpatient psychotherapy was scheduled.

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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Psychogenic nonepileptic seizure: A neurologist's perspective

When first meeting a patient with psychogenic nonepileptic seizure (PNES), physicians are presented with a tremendous opportunity to pave the way toward recovery. Astute primary care and emergency medicine physicians may suspect the diagnosis and initiate swift referral to a neurologist, and the neurologist can then confirm the diagnosis promptly and definitively with inpatient video electroencephalography (EEG). Together, these teams can shorten the interval between the onset of PNES and the initiation of psychiatric therapy, maximizing the chance for a successful outcome.

See related article, page 252

Physicians can launch the patient on the road to recovery—or make matters worse

PNES differs from most other functional disorders in that video EEG provides a definitive diagnostic test result. Ongoing normal cerebral rhythms during a typical episode usually "prove" that the events are nonepileptic. Experienced neurologists can make the diagnosis of PNES with confidence based on typical features in the history, characteristic patterns of behavior during the episodes, and normal EEG during the episodes and at baseline. The diagnosis may be more challenging in patients who have both epileptic and nonepileptic seizures, but video EEG is a powerful tool that can clarify the difference between episode types.

A CRUCIAL CONVERSATION

However, confirming the diagnosis with video EEG is only the start of the journey. As Drs. Tilahun and Bautista eloquently point out in a well-crafted review in this issue of the *Journal*,[1] the greater challenge and opportunity lie in how physicians present the diagnosis to the patient and family. At this critical juncture, the neurologist can either help launch the therapeutic process in a positive direction or worsen the psychiatric condition by invoking anger or confusion.

As pointed out by Tilahun and Bautista,[1] the key elements for this crucial conversation are empathy and clarity. Reviewing the patient's EEG tracings together and explaining their positive diagnostic value can allay doubt and fears that a medical diagnosis is being missed. Acknowledging the role of emotions and stress in producing real physical symptoms can help with acceptance of the PNES diagnosis. This in turn can lead to relief that antiseizure medication will not be necessary, and that the episodes can be effectively treated with the help of a psychiatrist or psychologist. Accomplishing these goals is important for a smooth transition of care to the mental health team.

Developing some personal language for the discussion can ensure that the results are positive. The delivery that I have developed in my own practice over the years includes the following elements:

Before the video EEG is performed, I set some expectations. "The episodes you are experiencing could be due to epilepsy, which involves a disturbance in the control system for the electrical activity of the brain, or it could be due to a mind-body interaction caused by stress and tension, even if we don't know right now what those stresses might be. As you can imagine, the treatment of the episodes will be very different depending on which turns out

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to be the case. Video EEG testing will give us the answer, and then we will know exactly how to proceed to solve the problem and help you get back to your everyday life."

Once the video EEG is complete and the diagnosis of PNES is confirmed, we can take the discussion further. "We are delighted to report that the EEG has given us good news. We were hoping that it would not show evidence of epilepsy, and in fact that was the case. Your EEG showed healthy, normal brain rhythms during the entire recording time, including during the episodes that you identified as typical of what you are experiencing at home. We are happy that we are not dealing with a new diagnosis of epilepsy, and that there is no need for treatment with antiseizure medication. The next step is for us to consult our expert colleague in psychiatry, who will help you develop a plan to stop the episodes by quieting and controlling the mind-body reflex that is causing the problem."

My experience is that most patients and families will accept the diagnosis when it is so presented and express willingness to meet with the psychiatrist or psychologist.

CAN ALSO PRESENT IN CHILDREN

Tilahun and Bautista[1] focus primarily on adolescents and adults. While most patients present between the ages of 15 and 35, PNES may also occur in children as young as 6 to 8 years old.[2–6]

Underlying factors include severe environmental stress such as violence or sexual abuse, or less severe conditions such as anxiety or school refusal (school avoidance). Mood disorders are also common in children with PNES and should be considered in every case.

The prognosis for resolution of PNES with treatment appears to be better in children than in adults, perhaps because the causes are often external to the child and amenable to prompt intervention.

AN EXCITING TIME

This is an exciting time for the management of PNES. The emergence of evidence-based psychotherapy has been a tremendous advance.[1] By confirming PNES with video EEG, presenting the diagnosis with clarity and empathy, and guiding patients toward specialized evidence-based psychotherapy, neurologists can help more adults and children than ever before to experience an improved quality of life. The review by Tilahun and Bautista[1] adeptly highlights these opportunities.

DISCLOSURES

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REVIEW

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Palliative care: An update for internists

ABSTRACT

All clinicians should maintain basic skills in general palliative care to help address the needs of patients and families. Because keeping up with the information provided by the growing palliative care literature can be challenging, we conducted a detailed search via Medline for palliative care articles published in 2020 in top peer-reviewed medical journals. Using a consensus-driven process of selection, we reviewed and summarized 11 articles to enhance knowledge of the practice-changing palliative care literature for general internists.

KEY POINTS

Transitions in health status provide important opportunities for internists to engage in advance-care planning with patients and complete physician orders for life-sustaining treatment (POLST) forms to improve delivery of goal-concordant care.

Internists can look for opportunities to improve patients' healthcare experience near end of life and reduce healthcare utilization by considering palliative care involvement for patients with non-cancer diagnoses.

Internists should be aware of the implications of COVID-19 on older adults' experience of loneliness and social isolation and its associated health consequences.

Patients with advanced cancer may benefit from as-needed olanzapine for chronic nausea or methylphenidate for fatigue.

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Palliative care (PC) uses an interdisciplinary approach to optimize quality of life and goal-concordant care for patients and families facing serious illnesses. With increasing age and therapies for cancer and other chronic diseases, the need for PC at a population level is significant.[1] Internists are frequently called upon to address PC needs of patients, including advance-care planning, symptom control, and providing goal-concordant care.[2] Yet keeping up with the growing PC literature is challenging.

This article reviews important PC research articles published between January 1 and December 31, 2020, using a case-based format. After performing a Medline keyword search of PC terms (palliative, pain, end-of-life, symptom management, communication, hospice, terminal illness, advanced directives) of 15 leading peer-reviewed PC journals, all identified articles were reviewed, and 11 articles[3–13] were selected for inclusion by ranking and consensus discussion based on the following factors: PC content, scientific rigor, impact on practice, and relevance to general medicine.

PALLIATIVE CARE FOR NON-CANCER ILLNESSES

Background

While most PC interventions involve patients with cancer, many patients with chronic non-cancer diagnoses also need significant coordinated and appropriate healthcare, especially at end of life.[14]

A meta-analysis and systemic review by Quinn et al[3] measured the association between

healthcare use, quality of life, and symptom burden in PC interventions for adults with non-cancer illnesses.

Findings

The analysis included 28 PC intervention trials for heart failure, chronic obstructive pulmonary disease, and dementia.[3] PC, compared with usual care, involved less emergency department use (20% vs 24%; odds ratio [OR] 0.82, 95% confidence interval [CI] 0.68–1.00) and fewer hospitalizations (38% vs 42%; OR 0.80, 95% CI 0.65–0.99). PC was not associated with improved quality of life (pooled standardized mean difference [SMD], 0.18, 95% CI, –0.24 to 0.61) and was associated with lower symptom burden, especially with interdisciplinary team involvement (pooled SMD –0.12, 95% CI, –0.20 to – 03). PC was also associated with more advance-care planning compared with usual care (38% vs. 42%, OR 2.95, 95% CI 1.52–5.73).[3]

Implications

Although it is unclear what aspects of PC influenced outcomes, PC interventions can help reduce emergency department use, hospitalizations, symptom burden, and increase advance-care planning for non-cancer diagnoses.

PALLIATIVE CARE CONSULTATIONS REDUCE BURDENSOME INTERVENTIONS

Background

Patients near end of life have higher intensity of care that does not necessarily lead to better outcomes.[14] Unpredictable disease trajectories associated with non-cancer diagnoses pose challenges in determining when to pursue a comfort-based approach.[15]

In this population-matched Canadian cohort study, Quinn et al[4] measured the association between newly initiated PC in the last 6 months of life and healthcare use and location of death in adults dying from non-cancer vs cancer illnesses. Secondary outcomes included the rates of potentially burdensome interventions such as positive pressure ventilation, cardiopulmonary resuscitation, and initiation of dialysis.

Findings

PC involvement in patients dying from non-cancer illness related to chronic organ failure was associated with 12% reduction in both emergency department visits (adjusted rate ratio [ARR] 0.88, 95% CI 0.85–0.91) and hospital admissions (ARR 0.88, 95% CI 0.86–0.91); 41% reduction in intensive care unit (ICU) admissions (ARR 0.59, 95% CI 0.56–0.62); and increased odds of dying at home or nursing home vs dying in hospital (OR 1.67, 95% CI 1.60–1.74).[4] Rates of potentially burdensome interventions were lower for those receiving PC (OR 0.66, 95% CI 0.64–0.69). Similar results were found for cancer patients. Unexpectedly, PC increased rates of emergency department visits (ARR 1.06, 95% CI 1.01–1.12) and hospital admissions (ARR 1.33, 95% CI 1.27–1.39) in patients dying from dementia. However, differences in these outcomes depended on patients' primary residence (nursing home vs. community). No association was found between healthcare use and PC for dementia patients living in the community compared with those in nursing homes. Community-dwelling dementia patients also had increased odds of dying at home (OR 1.35, 95% CI 1.23–1.49). The study only measured physician-led PC interventions; non-physician PC interventions could not be extrapolated.[4]

Implications

Like cancer, non-cancer diagnoses can benefit from specialty PC interventions at end of life and have the potential to reduce healthcare use and burdensome interventions.

Palliative care interventions can reduce emergency department use, hospitalizations, and symptom burden for patients with non-cancer diagnoses

TREATMENT-LIMITING PHYSICIAN ORDERS FOR LIFE-SUSTAINING TREATMENT

Background

While treatment-limiting physician orders for life-sustaining treatment (POLSTs) have been shown to ensure patient treatment preferences and thereby reduce some burdensome interventions at end of life,[16] association with ICU care is less understood.

Lee et al[5] conducted a retrospective cohort study of decedents with preexisting POLSTs who were hospitalized within 6 months of death to evaluate the association of POLSTs for medical interventions and ICU admission.

Findings

Of the 1818 decedents, ICU admissions occurred in 31% (95% CI, 26%–35%) with comfort-only orders, 46% (95% CI 42%–49%) with limited-intervention orders, and 62% (95% CI 58%–66%) with full-treatment orders.[5] Patients with comfort-only or limited-intervention POLSTs were less likely to receive ICU admission (comfort only, ARR 0.53 [95% CI 0.45–0.62]; limited interventions, ARR 0.79 [95% CI 0.71–0.87]). However, 38% (95% CI 35%–40%) of patients with treatment-limiting POLSTs received POLST-discordant care. Factors associated with lower likelihood of POLST-discordant care were dementia with comfort-only orders, cancer, and older age. Traumatic injury was associated with a higher likelihood of POLST-discordant care. The incidence of POLST-discordant intensive care did not decrease significantly over the 8 years of study (comfort only, ARR 1.01 per year [95% CI 0.94–1.09; $P = .70$]; limited interventions, ARR 1.00 per year [95% CI 0.96–1.04; $P = .90$]).[5]

Implications

Treatment-limiting POLSTs were associated with lower rates of ICU admission compared with full-treatment POLSTs. As 38% of patients received POLST-discordant care, further work is necessary to help provide patients with goal-concordant care at end of life. Further, as the study excluded patients not hospitalized prior to death, this may over-estimate the overall prevalence of goal-discordant care.

Treatment-limiting physician orders for life-sustaining treatment were associated with lower ICU admissions

EARLY PALLIATIVE CONSULTS CLARIFY PATIENT ICU GOALS-OF-CARE

Background

Although PC appears to improve quality of life for patients,[17] studies of PC impact in the ICU are mixed with varying study designs and measured outcomes.

Ma et al[6] employed a single-center cluster, randomized crossover trial with 6-week washout period to determine if early triggered multidisciplinary PC consults in the ICU would improve end-of-life outcomes. They used predetermined criteria to select patients at high risk of mortality who were randomized to PC consultation by an interprofessional team within 48 hours of ICU admission vs standard care.

Findings

Of the 233 enrolled patients, 199 (97 intervention, 102 control) were eligible to be analyzed, and the primary outcome of transition to do-not-resuscitate/do-not-intubate was significantly more frequent (50.5% vs 23.4%, $P < .0001$) and occurred earlier ($P < .0001$) with PC intervention in both unadjusted and adjusted models.[6] For secondary outcomes, transfer to hospice occurred significantly more frequently (18.6% vs 4.9%, $P = .0026$), and mechanical ventilation was of shorter median duration (4 vs 6 days, $P = .0415$) with PC intervention. There was no significant change in hospital, ICU, and 30-day mortality or hospital or ICU length of stay.[6]

Implications

Early targeted interprofessional PC consultations in the ICU increased transitions to do-not-resuscitate/do-not-intubate by hospital discharge, increased hospice referrals, and reduced days on mechanical ventilation. Further study is warranted to fully understand the cost implications of routine PC consultations in the ICU.

BRIEF COACHING SESSIONS CAN IMPROVE RESIDENT COMMUNICATIONS OF GOALS OF CARE

Background

In teaching hospitals, resident physicians frequently initiate goals-of-care discussions and facilitate end-of-life care but may feel uncomfortable with these discussions.[18]

Rodenbach et al[7] aimed to improve internal medicine resident PC skills through 2 didactics and thrice-weekly coaching sessions (averaging 16 minutes per session) during inpatient rotation. Residents completed pre- and post-rotation surveys of their preparedness in discussing PC topics.

Findings

Residents rated coaching sessions as useful and reported improved preparedness in goals-of-care conversations.[7] Residents asked questions centered on the following PC topics: communication (68.3%), pain (9.7%), non-pain symptoms (9.2%) and ethics (4.9%). During the 14-month intervention period, 42 residents cared for 232 at-risk patients (those

> 65 years with ≥ 2 hospitalizations in past 6 months or any patient > 90 years). Among at-risk patients, documented goals-of-care discussions rose from 5.2% to 12.9% before hospitalization, and from 25.0% to 57.3% before discharge. Rates of POLST completion did not differ between pre-intervention and intervention groups.[7]

Implications

Brief coaching sessions can integrate PC education into a busy clinical service, improve resident preparedness, and increase likelihood that residents will facilitate and document goals-of-care discussions with hospitalized patients.

3 WISHES PROJECT (3WP): ENHANCE PATIENT DIGNITY, REFLECT PATIENT IDENTITY, AND HONOR END-OF-LIFE PREFERENCES

Background

The 3 Wishes Project (3WP) elicits and implements wishes from dying ICU patients, family members, and clinicians to celebrate the legacy and life of patients through acts of compassion.[19]

Vanstone et al[8] completed a mixed-methods study with 730 patients from 4 North American, tertiary care ICUs, eliciting 3,407 (from 11 wish categories) and implementing 3,325 wishes. Qualitative data were gathered from 75 family members, 72 clinicians, and 20 managers or hospital administrators.

Findings

The value of 3WP included family honoring the lives and legacies of loved ones while inspiring compassionate clinical care.[8] Examples of performed wishes included dressing the patient in their own clothing, having a celebration in the patient's room, and providing transportation to enable others to visit the patient in the hospital. Family members reported an enhanced care experience with redirection of attention from the illness to the person's identity. Transferability factors included family appreciation and a collaborative ICU culture committed to dignity-conserving end-of-life care. 3WP was affordable (mean cost $5.19 per wish) after minimal investment for reusable materials. Each site sustained 3WP after study completion. Cultural sensitivity and adaptation may be needed for more vulnerable, diverse, or disadvantaged populations.[8]

Implications

When championed by compassionate local clinicians, 3WP is a valuable, transferrable, affordable, and sustainable program at end of life in the ICU.

COVID-RELATED LONELINESS AND END OF LIFE

Background

Loneliness is the subjective feeling of being left out, isolated, and lacking companionship, afflicting up to 32% of adults over age 55.[20–23] It is associated with increased rates of depression, functional decline, cognitive decline, and premature death.[21–23] Older adults with multimorbidity, recent life transitions, shrinking social networks, and poor socioeconomic status are frequently at risk for loneliness.[20–24] The COVID-19 pandemic has been associated with increased risk of loneliness in older adults.[24]

Abedini and colleagues[9] explored the relationship of loneliness end-of-life experience in older adults by conducting a secondary data set analysis of the Health and Retirement Study, a nationally representative, longitudinal survey of lonely and non-lonely American decedents over age 50 who died between 2004 and 2014 (n = 8,700). Postmortem interviews were performed with next-of-kin after participant death.

The 3 Wishes Project includes honoring the lives and legacies of loved ones while inspiring compassionate clinical care

Findings

Approximately one-third of the 2,896 decedents (34%) were lonely near end of life.[9] Lonely older adults had statistically significant higher odds of suffering from pain, difficulty breathing, severe fatigue, and confusion in the last year of life, were more likely to have higher total symptom burden at end of life, more likely to die in a nursing home rather than at home (ARR 1.78; 95% CI, 1.30–2.42), and more likely to use life support in the last 2 years of life (ARR 1.36; 95% CI, 1.08–1.71). This study was limited by its cross-sectional design and inability to assess causality.[9]

Implications

While this study was not conducted during the COVID-19 pandemic, loneliness is associated with higher symptom burden and poorer end-of-life outcomes. Given COVID-19 has exacerbated social isolation and loneliness,[24] clinicians should consider screening for and documenting loneliness routinely across care settings to identify high-risk older adults.

FAMILY VISITATION REDUCES POSTOPERATIVE DELIRIUM AFTER SURGERY

Background

Delirium affects up to 50% of older hospitalized adults, increasing hospital length of stay, functional decline, risk of subsequent dementia, and mortality, all leading to $164 billion in annual healthcare costs in the United States.[25,26] Multimodal, nonpharmacologic interventions like Hospital Elder Life Programs (HELP) have been shown to improve postoperative delirium outcomes, but typically rely on volunteers.[25,26]

Wang and colleagues[10] evaluated whether family rather than volunteer-based HELP programs could reduce postoperative delirium and associated complications. They conducted a single-blind, cluster randomized control trial in patients over age 70 on 6 surgical floors in a Chinese hospital assessing tailored-HELP intervention vs usual care. Families received education and nurse supervision as part of the intervention.

Use of family caregivers in Hospital Elder Life Programs reduced postoperative delirium and improved outcomes in older hospitalized patients

Findings

Of the 281 patients enrolled, postoperative delirium occurred in 2.6% of intervention patients vs 19.4% in usual care patients (RR 0.14, 95% CI 0.05–0.38).[10] Intervention patients had significantly less functional decline and cognitive decline at discharge, and mean length of stay was 4.26 days shorter. Generalizability is limited as China has higher numbers of patients per nurse, longer length of stay owing to lack of post-acute care facilities, and surgeons less commonly perform surgery on frail patients. Hence, the patient population may have been younger and possibly more robust compared to the United States population.[10]

Implications

Use of family caregivers rather than volunteers as participants in HELP interventions can reduce postoperative delirium and improve outcomes in older hospitalized patients in China. While this study did not evaluate the implications of COVID-19 on family-based interventions, other studies have shown that visitor restriction during the COVID-19 pandemic is associated with increased incidence of delirium,[27] and hence involvement of family should be considered to help reduce postoperative delirium.

PHYSICIAN ENGAGEMENT WITH INTERPRETERS FOR END-OF-LIFE CONVERSATIONS

Background

Approximately 26 million people living in the United States have limited English-proficiency that can negatively impact their healthcare experience and outcomes.[11,28,29] Use of medical interpreters in language-discordant patient encounters improves outcomes,[28,29] but little is known about the views of medical interpreters around best practices for end-of-life conversations.

Silva and colleagues[11] conducted 12 semi-structured interviews with Spanish and Chinese interpreters at a New York City hospital.

Findings

Qualitative analysis demonstrated that interpreters felt conflict between the need to translate words directly vs portraying messages in a culturally appropriate manner.[11] They felt high emotional burden when unprepared, and expressed challenges with interpreting end-of-life terms that are not commonly used in their culture (ie, do-not-resuscitate, intubation, resuscitation, PC).[11]

Implications

In-person interpretation should be used whenever possible for end-of-life conversations. Pre-meetings and debriefings can ensure that interpreters are prepared for challenging end-of-life conversations with reduced emotional burden. Interpreting within the normative cultural context rather than literal translation should be emphasized.

OLANZAPINE IMPROVES CHRONIC NAUSEA IN ADVANCED CANCER

Background

Chronic nausea is a distressing symptom in advanced cancer. While case reports and retrospective data suggest olanzapine may be helpful, there have been limited data from randomized control trials.[30]

Navari et al[12] conducted a multicenter, double-blind, placebo-controlled pilot randomized control trials to study the use of olanzapine (5 mg/day orally) for chronic nausea in 30 patients (15 per arm) with advanced incurable cancer who continued to have chronic nausea ≥ 7 days after completing chemotherapy or radiation therapy. Patients were permitted to use their prior anti-emetics as needed. Numerical scores for symptom intensity (appetite, nausea, fatigue, sedation, pain, well-being) and number of vomiting episodes were measured daily for 7 days.

Findings

Median nausea scores improved at day 1 in olanzapine arm to 2 (range, 2–3) compared with 9 (range, 8–10) in placebo arm.[12] The reduction in nausea scores in olanzapine arm was 8 points (95% CI, 7–8, $P < .001$) more than the placebo arm at 1 week. Additionally, olanzapine reduced vomiting, fatigue, pain and improved appetite and well-being (all $P < .05$). No adverse events were reported. After the protocol was broken, nearly all placebo patients transitioned to olanzapine with marked efficacy and minimal toxic effects. Patients only discontinued olanzapine when they were unable to take oral medications or died. While this pilot study had a small sample size, it did show substantial symptomatic improvement.[12]

Implications

Olanzapine 5 mg daily is effective and well-tolerated for chronic nausea and vomiting associated with advanced cancer.

METHYLPHENIDATE IMPROVES FATIGUE IN ADVANCED CANCER

Background

Fatigue is a common symptom that impacts quality of life in advanced cancer. Systematic reviews of methylphenidate for cancer-related fatigue have shown statistically significant reduction in fatigue, although less often clinically significant to patients.[31]

Pedersen and colleagues[13] conducted a prospective, controlled, double-blind, paired design study to evaluate the efficacy of methylphenidate as needed for management of fatigue in advanced cancer. Inpatient PC patients at a single institution in Denmark received a box of randomly arranged tablets of 10-mg methylphenidate or placebo to take in predetermined order up to every 3 hours as needed for fatigue over the course of a week with subsequent measures of symptoms 2 and 5 hours after tablet administration.

Findings

Twenty-eight of 38 enrolled participants were evaluable.[13] Mean change (decrease) in tiredness scores (on a 100-point visual analogue scale) at 2 and 5 hours was 20 and 17 after methylphenidate administration and 8 and 5 after placebo administration, respectively. Comparing mean differences, a significant decrease for methylphenidate compared with placebo was observed after 2 ($P = .004$) and 5 hours ($P = .001$), respectively. Methylphenidate was also significantly more effective compared with placebo regarding secondary measures of drowsiness and activity at 2 hours ($P < .001$ and $P = .008$, respectively). No serious adverse events were reported. Limitations of the study are short follow-up time, and the 3-hour interval of tablet administration may not have been long enough for washout of the prior tablet.[13]

Implications

10 mg of methylphenidate as needed provided statistically and clinically significant impact on fatigue scores in PC patients with advanced cancer. Studies of longer duration are needed.

A small pilot study of olanzapine showed symptomatic improvement for chronic nausea and vomiting associated with advanced cancer

CONCLUSION

Recent PC research provides important guidance to general medicine clinicians in symptom management, advance-care planning, and communication training in order to maximize compassionate care to patients and family members with serious illness. ■

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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Esophageal adenocarcinoma: A dire need for early detection and treatment

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ABSTRACT

Esophageal cancer is the sixth most common cause of cancer-related death worldwide. Esophageal adenocarcinoma is the most common subtype of esophageal cancer in the United States, and its incidence has risen dramatically in the last few decades. Modern endoscopic and surgical techniques have significantly improved morbidity and mortality rates of patients undergoing treatment for esophageal cancer. However, most cases are diagnosed at a late stage when the prognosis is poor, emphasizing the need for an effective screening strategy. This clinical overview focuses on screening, multidisciplinary evaluation, and treatment of early esophageal adenocarcinoma.

KEY POINTS

The 2 major subtypes of esophageal cancer are squamous cell carcinoma and adenocarcinoma, and they have different clinical presentations and natural history. The incidence of adenocarcinoma of the esophagus has increased dramatically over the past few decades in the Western world.

There are currently no standard or routine screening tests for esophageal cancer. However, many tests are under investigation for screening patients at high risk.

Management of early esophageal adenocarcinoma is based on patient and tumor characteristics and available institutional expertise.

ESOPHAGEAL CANCER IS THE SIXTH most common cause of cancer-associated death worldwide, accounting for an estimated 1 in every 20 cancer deaths.[1] More than 500,000 new cases are reported every year.[1]

Worldwide, squamous cell carcinoma is the most common type of esophageal cancer, followed by adenocarcinoma, while small-cell carcinoma, melanoma, sarcoma, and lymphoma are rare. However, in Western countries, esophageal adenocarcinoma is much more common than esophageal squamous cell carcinoma (**Table 1**),[2] and its incidence is rapidly growing in developed countries owing in part to the rising prevalence of obesity and gastroesophageal reflux disease.

Esophageal adenocarcinoma has a favorable prognosis if diagnosed early, when it is isolated to the mucosal and submucosal layers of the esophagus. Unfortunately, most cases are diagnosed at a late stage, when the prognosis is dismal. The 5-year overall survival rate of patients with esophageal adenocarcinoma is less than 20%, comparable

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TABLE 1

Esophageal adenocarcinoma vs squamous cell carcinoma

	Adenocarcinoma	Squamous cell carcinoma
Proportion of esophageal cancers[a]	64%	29%
Risk factors	Barrett esophagus Gastroesophageal reflux disease Central obesity Age > 50 Male sex	Heavy alcohol consumption Smoking Hot tea consumption Nitrite consumption Head and neck cancer Tylosis (autosomal dominant syndrome, mutation in *RHBDF2* gene)

[a] Based on 2018 data from National Cancer Institute Surveillance, Epidemiology, and End Results Program, reference 2.

to that of patients who have liver, lung, or pancreas cancer.[3] Thus, there is a dire need for effective screening strategies to diagnose it earlier.

Treatment has primarily focused on resection, either surgical or, more recently, endoscopic. Radiation therapy and chemotherapy have historically been considered in patients in whom resection is less feasible because the cancer has already spread. For esophageal cancer in general, a multidisciplinary approach may help identify the best therapeutic strategy based on patient and tumor characteristics and local expertise.

This review provides strategies relevant to the subset of esophageal adenocarcinoma that is detected early, and highlights the need for a multidisciplinary approach.

Esophageal adenocarcinoma has a favorable prognosis if diagnosed early, but it usually isn't

RISK FACTORS

Obesity

A meta-analysis of over 16,000 cases confirmed a strong association between body mass index, obesity, and esophageal adenocarcinoma.[4]

Multiple risk factors

In another study, the prevalence of Barrett esophagus (the precursor lesion of esophageal adenocarcinoma) was found to have a positive linear relationship with the number of risk factors, which included gastroesophageal reflux disease, male sex, age over 50, family history of Barrett esophagus or esophageal adenocarcinoma, and obesity (defined as body mass index > 35 kg/m^2).[5]

Other, unreliable factors

Symptoms. Most patients with early-stage esophageal adenocarcinoma are over age 65 and have no symptoms. The esophagus, being a distensible tube, can accommodate smaller tumors that remain asymptomatic until the lesion grows to a significant size.

Since gastroesophageal reflux disease involves mostly the distal esophagus and gastroesophageal junction, 94% of cancers associated with Barrett esophagus are found below the tracheal bifurcation. Significant dysphagia in early lesions should raise suspicion of more advanced disease or, rarely, a concurrent nonmalignant cause such as peptic stricture, inflammation, or concurrent submucosal tumor.

Eosinophilic esophagitis causes chronic inflammation of the esophagus, raising concerns that it may increase malignant transformation. However, a recent large database study could find no relationship between eosinophilic esophagitis and esophageal cancer.[6]

Alcohol consumption does not appear to increase the risk of esophageal adenocarcinoma, and some studies suggest wine may actually be protective.[7]

WHO SHOULD BE SCREENED?

Barrett esophagus, the major precursor of esophageal adenocarcinoma, is believed to progress through pathologic stages, from metaplasia to low-grade dysplasia, high-grade dysplasia, and esophageal adenocarcinoma. The rise in esophageal adenocarcinoma and its poor prognosis in its advanced stages have

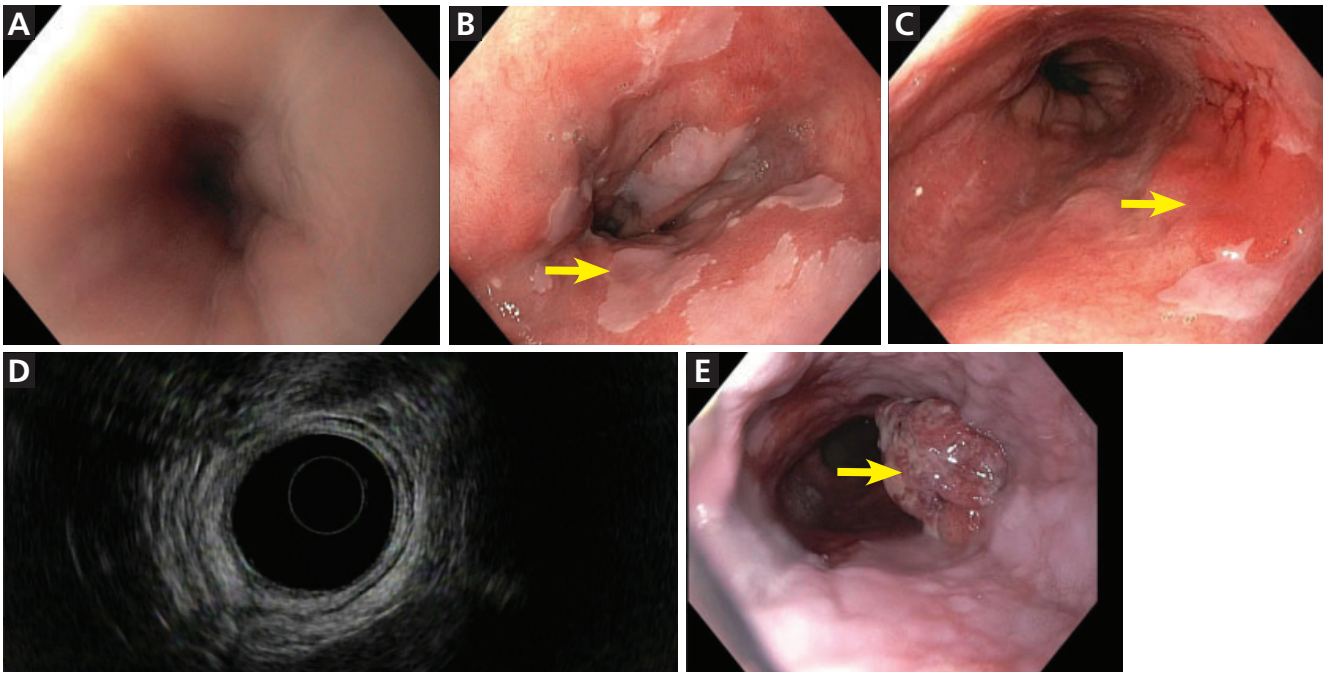

Figure 1. Endoscopic views of the esophagus. (A) Normal esophagus. (B) Barrett esophagus with islands of normal squamous mucosa (arrow). (C) Barrett esophagus with a discrete erythematous mass 4 × 2 cm (arrow) in the involved segment. (D) Barrett esophagus, endoscopic ultrasonographic view. (E) Esophageal adenocarcinoma (arrow).

raised interest in screening for Barrett esophagus and following it closely when discovered.[8]

In a prospective study, when patients with Barrett esophagus underwent endoscopic surveillance, the cases of esophageal cancer that arose were diagnosed at an earlier stage than in the general population.[9] However, studies have failed to identify an accurate, cost-effective, widely applicable tool that can lower the mortality rate.

Current guidelines, which are based on low-quality evidence and expert opinion, restrict screening to a very specific patient population: ie, those with long-standing gastroesophageal reflux disease (> 5 years) and those with frequent reflux symptoms (weekly or more) with 2 or more risk factors for Barrett esophagus or esophageal adenocarcinoma.[10] These risk factors include male sex, age over 50, central obesity (a waist circumference > 102 cm or a waist-hip ratio > 0.9), current or past history of smoking, White race, first-degree family history of Barrett esophagus or esophageal adenocarcinoma, or hiatal hernia. Patients diagnosed with Barrett esophagus without dysplasia should undergo endoscopy every 3 to 5 years.

In a large nationwide study, the annual risk of esophageal adenocarcinoma after a diagnosis of Barrett esophagus was 0.12%, much lower than the assumed risk of 0.5%, which is the basis for current guidelines.[11] However, nearly 90% of cases of esophageal adenocarcinoma are diagnosed in patients not known to have Barrett esophagus.[12] This shows that the current screening guidelines continue to miss a large number of patients at risk.

Upper endoscopy (Figure 1) is the gold standard for screening, but it necessitates sedation and is relatively expensive and inconvenient for a screening procedure. An ideal screening tool needs to be relatively inexpensive, well-tolerated, and applicable to general practice.

Detection rates of Barrett esophagus have been improved with advances in endoscopy such as high-definition imaging, chromoendoscopy (which uses special staining to enhance mucosal visualization), and narrow-band imaging (which enhances the mucosal resolution by selecting specific wavelengths of light).

Endoscopy is the gold standard for screening, but is expensive, inconvenient, and requires sedation

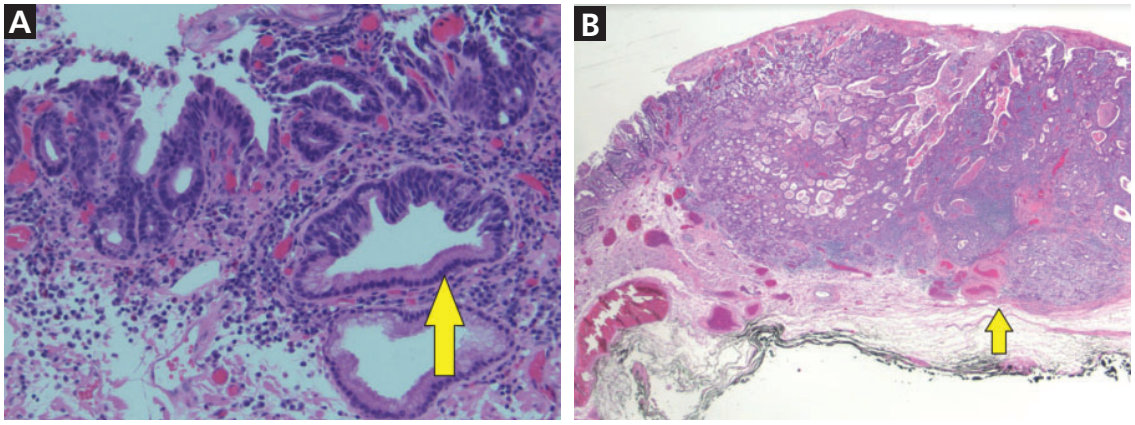

Figure 2. (A) High-grade dysplasia (arrow) from the periphery of a Barrett esophagus lesion (hematoxylin and eosin, magnification × 4). (B) Complex atypical glandular proliferation diagnostic of adenocarcinoma and involving the submucosa (arrow highlights submucosa) (hematoxylin and eosin, magnification × 20).

Swallow studies such as barium swallow do not allow for histologic assessment for metaplasia or dysplasia. Therefore, they must not be used for screening or surveillance of Barrett esophagus.

Newer screening methods for Barrett esophagus

Screening methods for Barrett esophagus that do not require endoscopy with sedation are under investigation.

Breath testing using an 'electronic nose' to screen for Barrett esophagus has shown promising results

Cytosponge (Medtronic) is an ingestible capsule containing a sponge attached to a string. The capsule dissolves on reaching the stomach and releases the sponge, which can be withdrawn from the esophagus out of the mouth by pulling the string. The sponge collects epithelial cells on its way out of the esophagus and is then tested for biomarkers of Barrett esophagus such as trefoil factor 3. Cytosponge is inexpensive and safe, and a prospective study found it to have a sensitivity of 73% and a specificity of 94% for detecting lesions measuring at least 1 cm.[13] A systematic review had similar findings.[14]

A swallowable balloon device can similarly sample the distal esophagus and detect DNA methylation markers. Its reported sensitivity in detecting Barrett esophagus metaplasia was 90.3% and its specificity 91.7%.[15]

Transnasal endoscopy, another office-based technique, uses a reusable endoscope with a disposable outer sterile sheath. It seems to be better tolerated than standard endoscopy while showing similar findings.[16]

Breath testing using an "electronic nose" to detect volatile organic compounds in exhaled air has shown promising results, with a sensitivity of 91% and specificity of 74%.[17]

These novel screening tools may prove to be efficient and cost-effective in primary care. However, more research is needed before they can be widely adopted. Clinical trials are under way to assess patient acceptance and preference for these different tools.

Possible preventive measures

Although epidemiologic studies suggested aspirin and nonsteroidal anti-inflammatory drugs might prevent Barrett esophagus and esophageal adenocarcinoma, clinical trials of these drugs to prevent esophageal adenocarcinoma have been unsuccessful.[18]

Retrospective data from multiple centers show that diets rich in antioxidants, fruits, vegetables, omega-3 fatty acids, polyunsaturated fat, and fiber are associated with lower risk of Barrett esophagus.[19,20]

BIOPSY IS THE GOLD STANDARD FOR DIAGNOSIS

On endoscopy, early lesions of esophageal adenocarcinoma can be flat, polypoid, or slightly depressed. Advanced tumors present as masses that may obstruct the esophageal lumen. The gold standard for diagnosing esophageal adenocarcinoma is tissue sampling by endo-

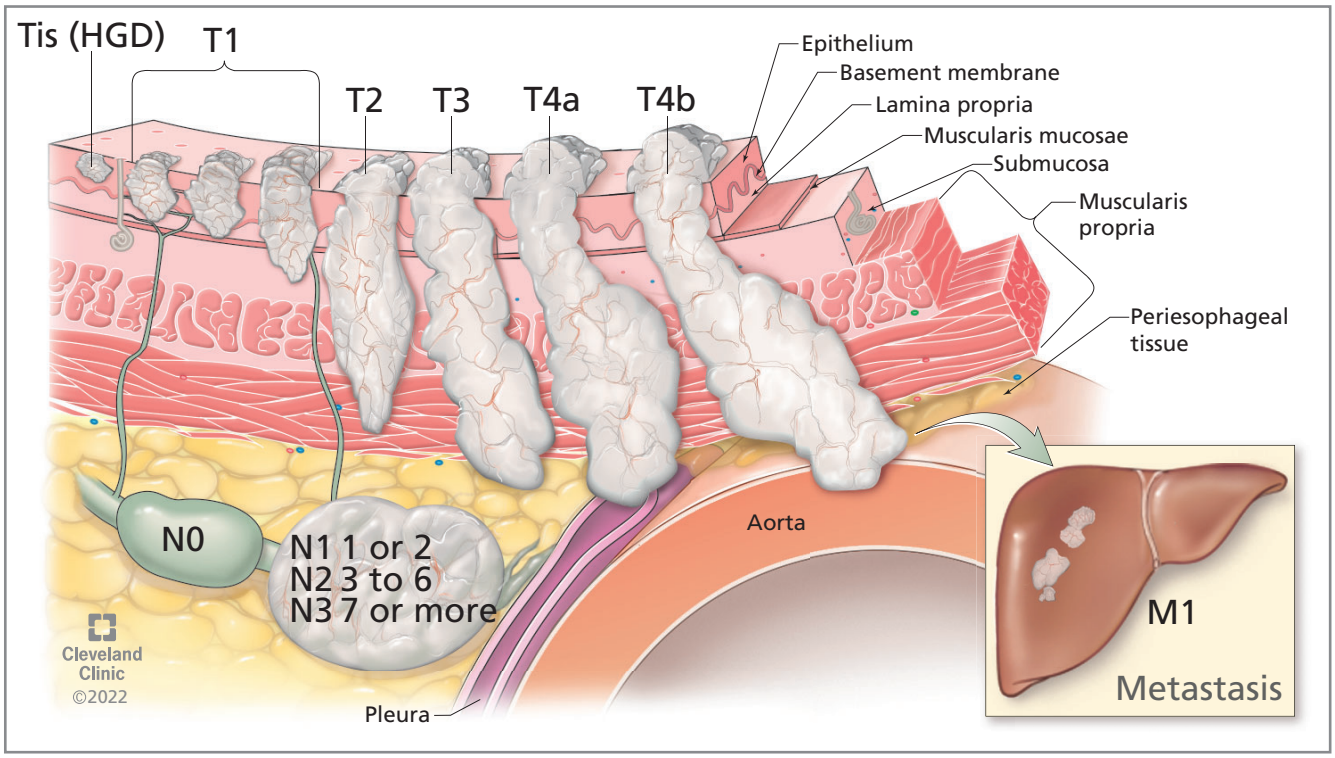

Figure 3. The tumor, node, metastasis (TNM) staging system for esophageal cancer helps determine prognosis and treatment based on tumor depth, number of affected lymph nodes, and metastasis to distant organs.

HGD = high-grade dysplasia

scopic biopsy (**Figure 2**). A prospective trial revealed a diagnostic accuracy of 93% with a single biopsy, and additional biopsy specimens increased the yield to over 98%.[21]

CANCER STAGING IS PARAMOUNT

Once esophageal adenocarcinoma is diagnosed, its stage needs to be assessed to determine prognosis and treatment. This involves the TNM system (**Figure 3**), as follows:

- **T**umor depth (categorized on a scale of Tis through T4b)
- **N**odes, ie, number of lymph nodes affected (categorized on a scale of N0 through N3)
- **M**etastasis in distant organs (M0 for no distant metastasis, or M1 for distant metastasis).

Positron emission tomography with computed tomography. The role of 18-fluorodeoxyglucose (FDG) positron emission tomography with computed tomography (PET/CT) and endoscopic ultrasonography in early esophageal adenocarcinoma staging is controversial. However, the National Comprehensive Cancer Network guidelines[22] recommend staging by PET/CT and endoscopic ultrasonography in cases of advanced cancer (≥ T1b) to evaluate for nodal spread.

PET/CT is less beneficial in early esophageal adenocarcinoma than in advanced disease. Some studies found that it could not reliably detect early esophageal adenocarcinoma stages such as T1a and T1b tumors.[23,24] A study of 79 patients with clinically staged T1a and T1b esophageal adenocarcinoma who underwent preoperative PET/CT showed all FDG-avid nodes seen were false positives[23]; another study had similar findings.[24] This suggests that PET/CT could lead to more unnecessary biopsies. However, if a tumor is found to be more advanced on pathologic study after endoscopic submucosal dissection, performing PET/CT after resection has limited utility, as inflammation of the resection bed is often FDG-avid on PET.

For this reason, we consider PET/CT before resecting bulky or borderline tumors

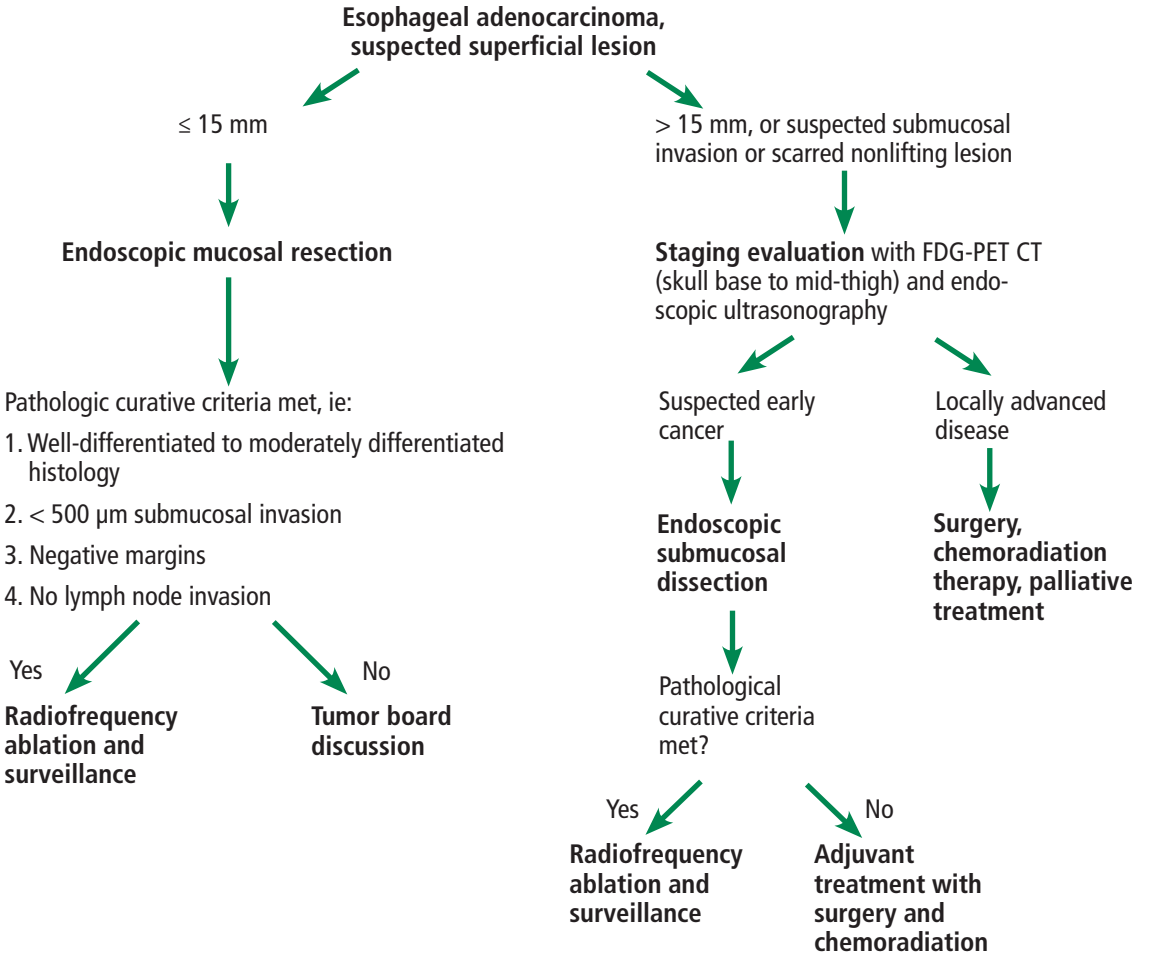

Figure 4. Our care path for early esophageal adenocarcinoma.

FDG-PET CT = 18-fluorodeoxyglucose positron-emission tomography with computed tomography

larger than 15 mm or lesions with suspected superficial submucosal invasion (SM1) greater than 500 µm.

Endoscopic ultrasonography can assess for the depth of tumor invasion and locoregional lymph node spread. However, it has a high false-positive rate of up to 10%.[25] Consequently, the American Society for Gastrointestinal Endoscopy guidelines strongly recommend against its routine use in early esophageal adenocarcinoma to stage mucosal (T1a) and submucosal (T1b) disease.[10]

These days, more advanced tumors are being referred for endoscopic resection. Thus, accurate staging and ruling out advanced disease before proceeding with endoscopic treatment is paramount. Further research is required to understand the role of PET/CT and endoscopic ultrasonography in large T1a (> 15 mm) and early T1b disease that is increasingly being elected for endoscopic resection.

TREATMENT OPTIONS

Our suggested care path for early esophageal adenocarcinoma is shown in **Figure 4**.

Surgery

For decades, the first-line treatment for early esophageal adenocarcinoma, including Barrett esophagus, has been open surgical resection. Technical advances in surgery such as robot-assisted minimally invasive esophagectomy, minimally invasive esophagectomy, and 3-dimensional imaging have improved re-

covery times and lymph node yield and have significantly decreased postoperative pain, intraoperative bleeding, and hospital length of stay.[26]

Minimally invasive approaches have become preferred, with long-term results that are not inferior to those of open esophagectomy. A study of more than 5,500 patients undergoing surgical resection showed a 90-day mortality rate of approximately 7%, which did not differ by surgical approach.[27] However, mortality rates were lower for patients with T1a tumors (3.1%) and T1b tumors (6.0%).[27]

The role of surgical esophagectomy remains controversial in early T1a tumors with high-risk features such as poor differentiation and large size, due to high rates of perioperative mortality (3%–6%) and morbidity, with a similar risk of locoregional spread (4.2%).[27] However, T1b tumors in otherwise healthy patients are considered for immediate esophagectomy due to the higher risk of lymph node metastasis (22%–28%).[28] In a 2020 study, esophagectomy for T1b tumors was found to be associated with higher rates of overall survival and histologic remission compared with endoscopic resection.[28] However, the patients treated endoscopically were older and had multiple comorbidities.

Postoperative surgical complications affect long-term mortality rates. Procedure-specific complications include conduit abnormalities, and recurrent laryngeal nerve injury; systemic complications include atrial fibrillation, myocardial infarction, and pneumonia. Long-term sequelae of esophagectomy include functional disorders such as dysphagia, delayed gastric emptying, reflux, and dumping syndrome. However, esophagectomy is usually well tolerated long-term with lifestyle changes such as eating frequent small-portion meals slowly and avoiding foods and beverages high in sugar.

Endoscopic surgery

Modern endoscopic techniques and devices have led to a shift to endoscopic treatment of early esophageal cancer rather than surgery, although not all early esophageal adenocarcinomas are amenable to curative endoscopic resection.

The esophageal architecture is unique in that the lymphatics penetrate through the muscularis mucosa and reach the lamina propria, leading to a theoretical risk of lymph node metastasis in early (T1a) tumors.[29] Barrett esophagus-related cancer involving the mucosa is believed to have a small risk (1%–2%) of lymph node metastasis, which increases with deeper invasion of the submucosa[30]:

- 7.5% with superficial submucosal invasion
- 10% with invasion in the middle third of the submucosa
- 45% with deep submucosal invasion.

Endoscopic resection can be considered in tumors at low risk for lymph node metastasis or in higher-risk tumors in patients who are medically unfit for surgery. The risks of perioperative death and of regional spread are between 3% and 4%.[29,31] Therefore, it is important to weigh the risk of lymph node metastasis and the risk of morbidity and mortality of surgery in a patient before deciding the best therapeutic approach for early esophageal adenocarcinoma.

There are 2 main endoscopic resection techniques: endoscopic mucosal resection and endoscopic submucosal dissection.

Endoscopic mucosal resection can be performed by 2 main methods: cap-assisted endoscopic mucosal resection (**Figure 5**), in which a cap is attached to the tip of the endoscope to depress mucosal folds and allow better visualization, and banding.[32] Esophageal endoscopic mucosal resection poses a 1.2% risk of bleeding, a 1% risk of stricture formation, and a low risk of perforation (0.2% to 1.3%).[33] The safety, success rates, and procedural ease of endoscopic mucosal resection have established it as a mainstay in the treatment of early esophageal adenocarcinoma. However, for larger lesions, endoscopic mucosal resection requires removing the tumor in multiple pieces, which is associated with higher recurrence rates.

Endoscopic submucosal dissection can allow removal of even larger tumors in a single piece (en bloc) and is associated with higher rates of cure and a lower risk of recurrence, and it allows for precise histopathologic analysis.[34–36]

A prospective trial comparing endoscopic mucosal resection and endoscopic submucosal dissection for Barrett esophagus and esophageal adenocarcinoma found the en bloc resection rate to be 100% with endoscopic submucosal dissection, but only 15% with endoscopic

Accurate staging is paramount before proceeding with endoscopic treatment

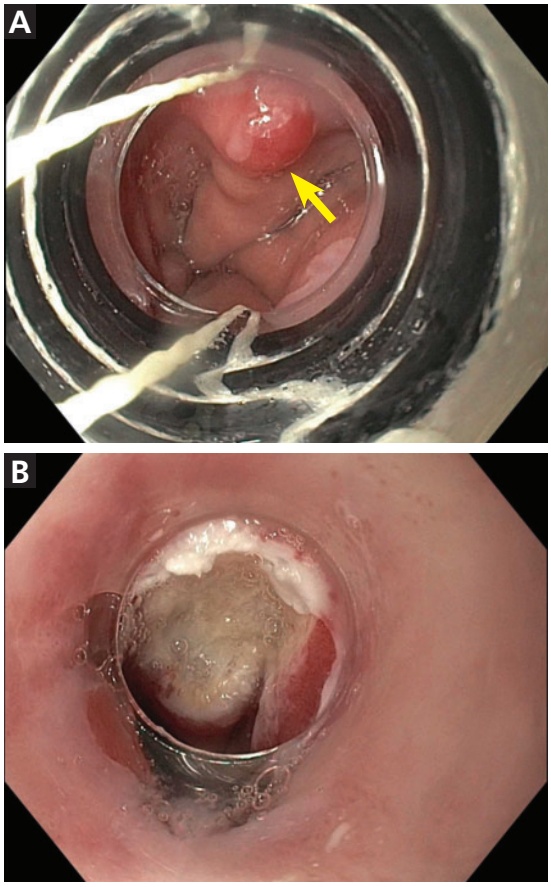

Figure 5. Band endoscopic mucosal resection of Barrett esophagus nodule. (A) Barrett esophagus nodule (arrow). (B) Resection bed after successful band endoscopic mucosal resection.

Radiotherapy alone can be an option for elderly patients who cannot undergo surgery or endoscopic therapy and concurrent chemotherapy

mucosal resection.[37] Likewise, a meta-analysis showed higher rates of R0 resection (margins free of neoplasia) (92.3% vs 52.7%) and lower rates of local recurrence (0.3% vs 11.5%) with endoscopic submucosal dissection than with endoscopic mucosal resection.[38]

Further information on these endoscopic techniques can be found in our earlier article in this Journal.[39]

Chemoradiation

Early esophageal adenocarcinoma (T1a, T1b) is primarily managed with endoscopic resection or surgery. However, recent evidence suggests that there may be a role for neoadjuvant (before resection) or adjuvant (after resection) chemoradiation therapy in early disease, particularly in patients with high-risk tumors (incomplete resection, positive deep margins, lymphovascular invasion, poorly differentiated tumors, tumors larger than 2 cm) who are medically unfit for surgery with lymph node dissection.[28]

The ChemoRadiotherapy for Oesophageal Cancer Followed by Surgery Study[40] included patients with T1 to T3 and N0 to N1 resectable esophageal adenocarcinoma and showed higher survival rates when patients underwent neoadjuvant chemoradiation therapy before surgery. Of note, data on this topic are limited by studies that included only patients with esophageal squamous cell carcinoma.

Paclitaxel and carboplatin are commonly used with concurrent radiotherapy. Another combination that is increasingly being used is 5-fluorouracil and oxaliplatin concurrent with radiotherapy. An ongoing randomized trial is comparing these 2 adjuvant regimens for resectable esophageal adenocarcinoma.[41]

Radiotherapy alone (external-beam or brachytherapy) can be an option for patients over age 65 with esophageal adenocarcinoma who cannot undergo surgery or endoscopic therapy and concurrent chemotherapy. The data on radiation treatment alone are primarily from retrospective series in patients with esophageal squamous cell carcinoma. Poor surgical candidates who are definitively treated with chemoradiation therapy can have residual, recurrent, or metachronous disease. These patients can be managed with salvage endoscopic submucosal dissection or ablation therapy.

Further study is needed to explore the utility of neoadjuvant or adjuvant chemoradiation therapy in early esophageal adenocarcinoma.[22]

Adjuvant treatment after noncurative endoscopic resection

Patients with early esophageal adenocarcinoma are increasingly being treated with endoscopic resection. However, some resections are noncurative, with poor differentiation, lymphovascular invasion, deep submucosal invasion, or positive margins. These patients are at higher risk of lymph node metastasis and progressive disease.

Ideally, esophagectomy with or without adjuvant chemoradiation therapy is the treatment of choice for these patients. However, patients who have high-risk features after endoscopic resection and who are poor surgical

candidates for definite esophagectomy with lymph node dissection can be referred for chemoradiation therapy.

A prospective trial in patients with T1a esophageal squamous cell carcinoma who underwent endoscopic submucosal dissection found a 3-year recurrence-free survival rate of 100% in those who received adjuvant radiotherapy and 85.3% in those who did not.[42] Interestingly, no severe radiation adverse events were noted.

Surveillance following curative endoscopic resection

In esophageal adenocarcinoma, endoscopic resection is considered curative if the resection histology is well-differentiated to moderately differentiated with no lymph node invasion, with less than 500 µm submucosal invasion combined with negative lateral and deep margins.[43] In comparison, squamous cell carcinoma endoscopic curative resection criteria include en bloc R0 resection of superficial lesions invading the lamina propria (T1a m2) with well-to-moderately differentiated histology with no lymphovascular invasion. En bloc R0 resection of a well-differentiated m3 or sm1 tumor (< 200 µm) without lymphovascular invasion has a low risk of lymph node metastasis, and these features are a relative indication for endoscopic submucosal dissection.[43]

Patients who undergo complete endoscopic resection of Barrett esophagus or esophageal adenocarcinoma are enrolled in a posttreatment surveillance program. Posttreatment surveillance is stratified based on postresection pathologic staging[44]:

For Barrett esophagus with high-grade dysplasia, upper endoscopy every 6 months for 2 years and then yearly is recommended.[45]

For T1a esophageal adenocarcinoma, endoscopic ultrasonography and CT can be considered, as these lesions have a 1% to 2% risk of lymph node metastasis. Surveillance consists of endoscopic ultrasonography every 6 months for 2 years, then endoscopic ultrasonography yearly and CT of the chest and abdomen yearly for 5 years.[45]

For higher-risk resections, surveillance includes endoscopic ultrasonography every 3 months for the first year followed by every 6 months for 1 year and then yearly. CT of the chest and abdomen is recommended at shorter intervals: every 6 months for the first year and yearly for the next 5 years.

THE BOTTOM LINE

Early esophageal adenocarcinoma is commonly diagnosed serendipitously in patients without symptoms undergoing upper endoscopy for other reasons. Due to the unique anatomy of the esophagus, even early esophageal adenocarcinoma has a risk of lymph node metastasis, and appropriate management is necessary.

For small esophageal adenocarcinoma lesions (ie, < 1.5 cm), multiple studies have shown endoscopic mucosal resection to be an effective strategy with good long-term results. For larger lesions or suspected deeper invasion or squamous cell carcinoma, a multidisciplinary approach is warranted. Endoscopic submucosal dissection can be effectively used to remove superficial tumors, despite their size or associated fibrosis. However, for lesions involving more than two-thirds of the circumference of the esophagus, there is a risk of esophageal stricture formation.

Patients with early esophageal adenocarcinoma and risk of lymph node metastasis are best treated with surgical resection, which allows for lymph node dissection, but many patients over age 65 or those with significant comorbidities may not be candidates for surgery. In these patients, endoscopic resection with adjuvant chemotherapy or radiotherapy can be considered. Some patients with early esophageal adenocarcinoma may not be candidates for either endoscopic or surgical resection owing to deep submucosal invasion, scarred disease, prior radiotherapy to the field, or severe comorbidities preventing anesthesia -for procedure. In these patients, neoadjuvant radiotherapy, brachytherapy, chemotherapy, or a combination of these can be performed. ■

Neoadjuvant or adjuvant chemoradiation may have a role in early disease

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Dr. Raja has disclosed intellectual property rights with Chromacode Inc and consulting for Smiths Medical. Dr. Kamath has disclosed consulting for Exelixis. Dr. Allende has disclosed acting as advisor or review panel participant for Incyte. Dr. Murthy has disclosed consulting and private ownership or partnership with Advanced Medical Solutions International. Dr. Bhatt has disclosed consulting for Aries Pharmaceuticals, Boston Scientific, Lumendi, and Medtronic, and intellectual property rights with Medtronic. The other 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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