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Continuous glucose monitoring: High-tech devices still need some low-tech backup

Salt-and-pepper skin pigmentation

Fixed drug eruption due to ibuprofen

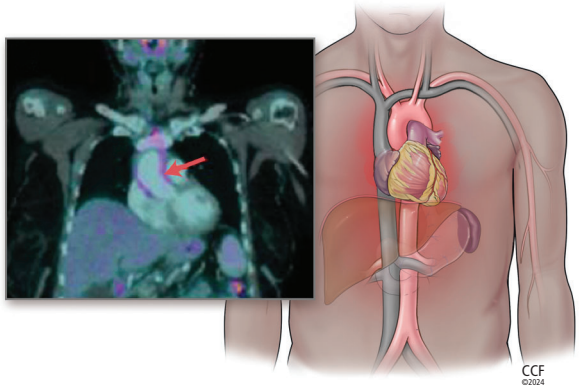
COMPLETE TABLE OF CONTENTS ON PAGE 583

Abdominal pain in a patient with epistaxis, telangiectasias, and arteriovenous malformations

Using continuous glucose monitoring data in daily clinical practice

Sorting out aortic aneurysms: A team enterprise

Incidentally detected noninfectious thoracic aortitis: A clinical approach



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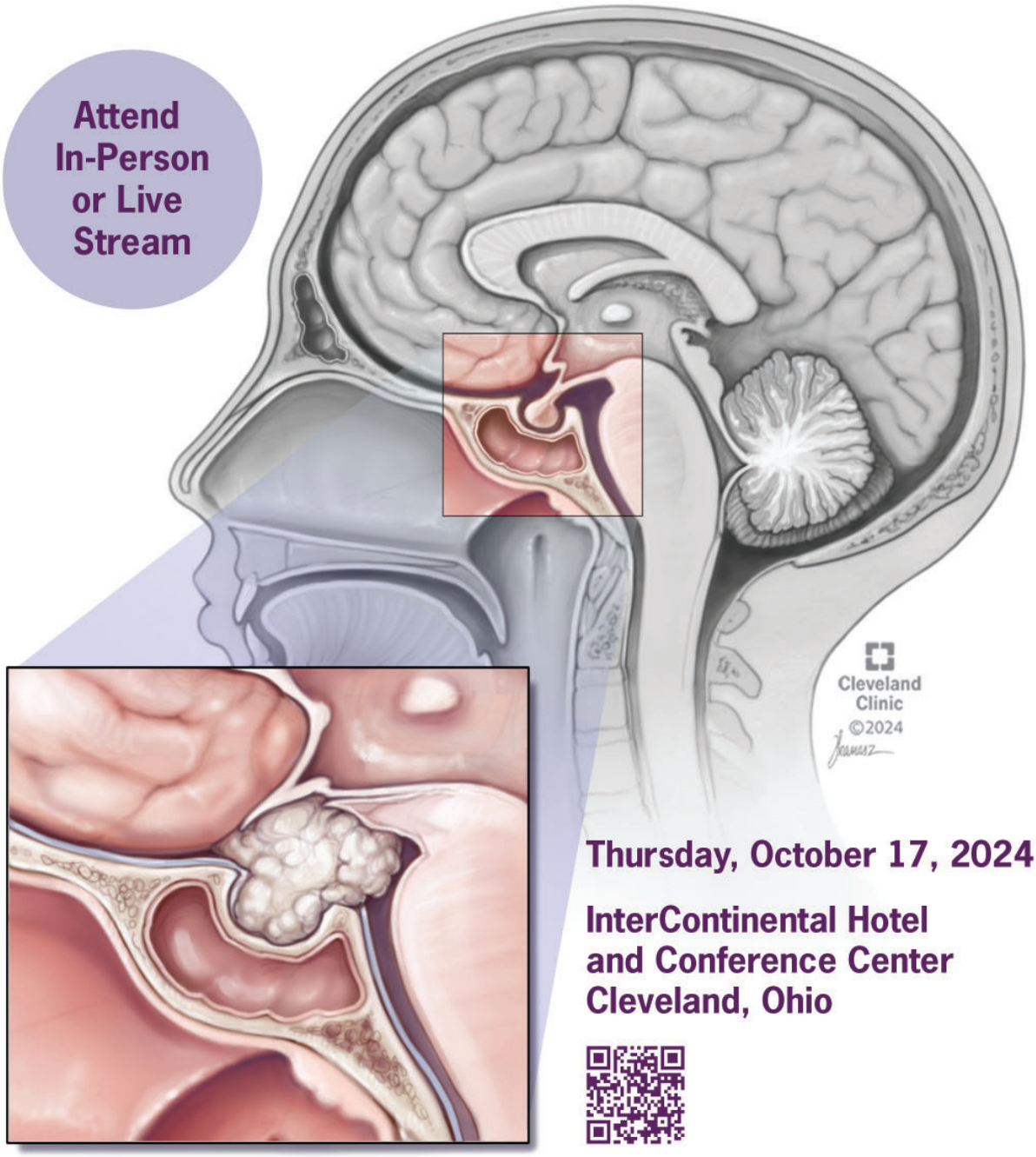

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Table of Contents

CONTINUED ON PAGE 584

Upcoming Features

- Cervical cancer screening in high-risk patients: Clinical challenges in primary care
- How do I manage my patients with thyrotoxicosis until they see the endocrinologist?

CONTINUED FROM PAGE 583

Continuous glucose monitoring: High-tech devices still need some low-tech backup

It doesn't take a lot of reflection to appreciate the dramatic effect that technology has played in reshaping our day-to-day behaviors. We carry computers in our pockets that can answer our verbalized questions that range from grocery store hours to the impact of *MTHFR* polymorphisms on the risk of developing psychiatric disorders. We don't need to carry change to use a "pay phone" to make an emergency call, and certainly don't need to consult a map or stop at a gas station to ask for directions (which of course many of us carrying the Y chromosome rarely did anyway).

But what happens when technology fails us—our phone battery dies and there is no available charger, or we enter the twilight zone where there is no signal? Without my phone, navigating beyond my home and work neighborhoods often becomes a challenge. I need to consciously think through potential driving routes, and I rarely can rely on visual clues because when I drive now I respond instead to the audible instructions issued in an Australian accent by my phone-based GPS app while focusing on the car in front of me. As inconvenient and potentially embarrassing as phone failures may be, they are not health-threatening, while failures of medical technologies that many of us increasingly rely upon on a day-to-day basis can be. And what if we don't recognize that our health monitoring device has not completely "failed," but is malfunctioning and is providing us with inaccurate data?

I recently got a phone call from my brother-in-law about his blood glucose "numbers." When he is not playing tennis, he works as a consultant for various companies analyzing large data sets. He has late-onset autoimmune diabetes for which he takes a cocktail of insulins and other medications, keeping his hemoglobin A1c around 6%. He called to discuss his suddenly out-of-control glucose "numbers," which included an early-morning value around 300 mg/dL that was not the result of a midnight Twinkie break. He had no symptoms (or monitor-reported glucose values) to suggest that these reflected a Somogyi effect, and, other than having been playing tennis outside in temperatures hovering in the high-90°F range, he had no reason to suspect a cognitive, behavioral, or systemic problem that might explain the hyperglycemia. A short chat and the mutual recognition that the "numbers" had not changed as they should have with an extra self-administered dose of short-acting insulin and a brisk walk led to him finding a lancet and test strip and discovering that his actual blood sugar was under 100 mg/dL. This was a sensor malfunction, not a primary medical issue.

Written instructions that come with the sensor and clinical practice guidelines recommend checking a fingerstick capillary glucose level when the monitor reports glucose values that don't jibe with symptoms or expectations. Even so, we wondered out loud how often this happens, and what might be the repercussions to someone busy with life activities who, with trust in their previously well-functioning technology, repeats their initial insulin bolus in response to an apparent

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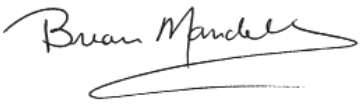
glucose of 300 mg/dL with a rising trend, which markedly drops their actual already normal blood glucose (potentially clouding their judgment), before considering a device malfunction.

The benefits of continuously collected and reported (in almost real time) interstitial glucose levels are many, as highlighted by Martens et al[1] in this issue of the *Journal*. Before my brother-in-law started using a monitor, he less often met his hemoglobin A1c target. But glucose monitoring device malfunctions and disruptions are not rare events. In a survey study (N = 99) that asked patients with diabetes who used glucose monitoring devices about adverse events due to monitor "disruption," hyperglycemia occurred 4 times or more in 37% of the surveyed patients.[2] Reported identified causes for monitor inaccuracy include poor insertion, poor adhesion, and local inflammation or infection.[3]

Thus, it is not a bad idea to regularly remind our patients, even the most astute ones, as they become increasingly reliant on high-end devices to monitor their physiology (glucose, blood pressure, heart rhythm, oxygen saturation), that their devices are not without occasional glitches, and they should be prepared to use a low-end backup monitoring alternative or have the "numbers" validated in a healthcare facility when the numbers go awry without obvious explanation.



Brian F. Mandell, MD, PhD
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October 17
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October 17–18
London, UK

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November 1–3
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Warrensville Heights, OH

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November 8
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CASE-BASED MANAGEMENT OF TRICUSPID AND MITRAL VALVE DISEASE
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March 6–9
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Salt-and-pepper skin pigmentation

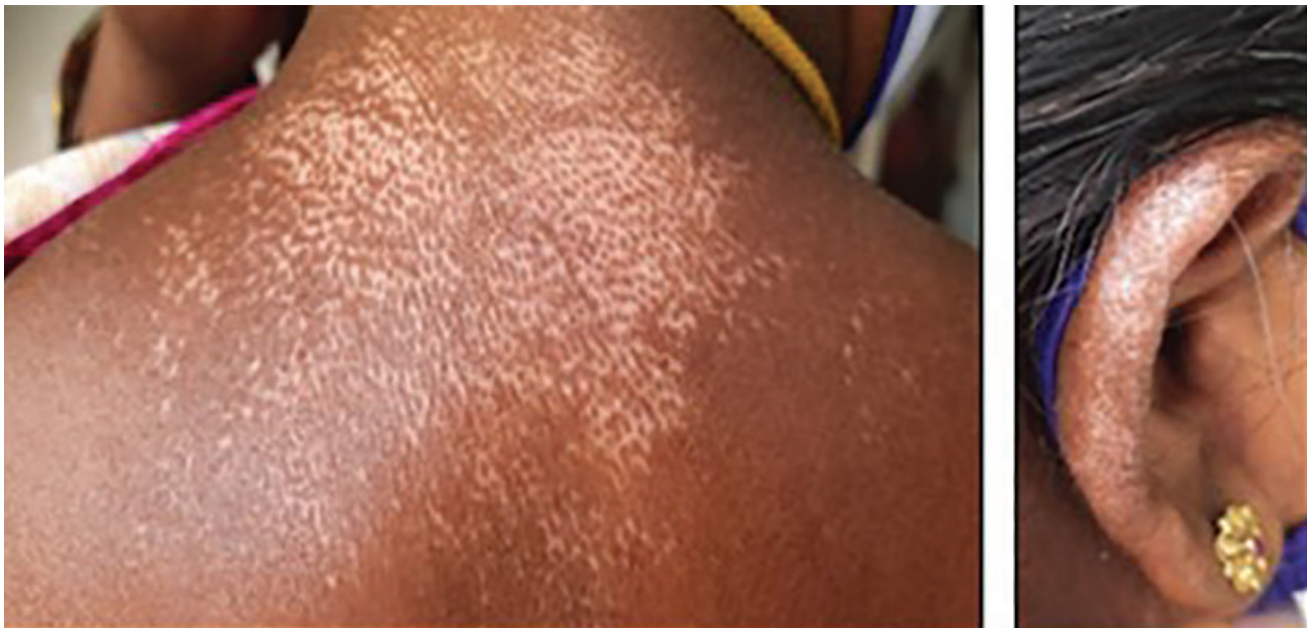

Figure 1. Salt-and-pepper skin pigmentation of the nape of the neck and pinna.

A 45-year-old female presented with an 18-month history of skin discoloration spanning the nape of the neck, ears, and scalp that was accompanied by itching. There was no history of hair dye use. She denied experiencing skin tightness, Raynaud phenomenon, fingertip ulceration, dysphagia, retrosternal burning, difficulty opening her mouth, dyspnea, palpitations, pedal edema, or joint pain.

During physical examination, the patient exhibited salt-and-pepper pigmentation on the nape of the neck, pinna of each ear, and scalp (**Figure 1**). There was no restriction in opening her mouth, binding down of the skin, ragged cuticles, or abnormal chest expansion.

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WORKUP AND DIAGNOSIS

Dermoscopy of the skin lesions revealed homogeneous depigmented areas with perifollicular pigmentation (**Figure 2**). The differential diagnoses considered were vitiligo repigmentation and early scleroderma. The patient did not have other lesions elsewhere on the body, and the oral mucosa was normal. Results of a routine laboratory workup including complete blood cell count and metabolic panel were within normal limits. However, antinuclear antibody was detected (1:320) in a centromere pattern. Chest radiography and pulmonary function test results were normal. Biopsy of skin from the nape of the neck revealed a focally thinned out epidermis with loss of rete ridges. The superficial dermis exhibited mild perivascular lymphocytic infiltrate, with appendages appearing pulled up and bound down.

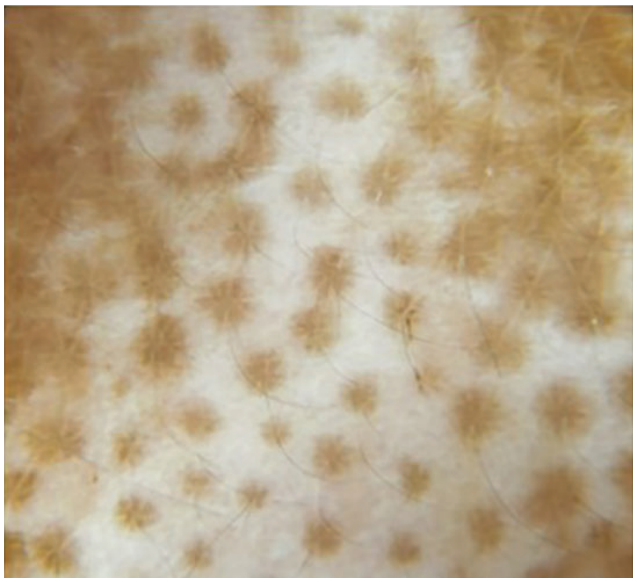

Figure 2. Homogeneous depigmented areas with perifollicular pigmentation.

Based on the classic skin lesion, absence of oral dyspigmentation, suggestive dermoscopic findings, and histopathologic findings consistent with scleroderma, a conclusive diagnosis of scleroderma was made.

The patient was started on methotrexate 0.3 mg/kg weekly to prevent cutaneous progression. On follow-up 4 months later, subjective improvement of the lesions was noted.

AN EARLY FEATURE OF SYSTEMIC SCLEROSIS

Systemic sclerosis is an autoimmune rheumatic disease characterized by chronic inflammation and fibrosis affecting the skin, gastrointestinal system, microvasculature, lungs, and heart.[1] Presence of anticentromere antibody is usually associated with limited cutaneous disease and less chance of systemic involvement.[2] Skin involvement manifests as areas of thickening, fibrosis, and, in some patients, a distinctive dyspigmentation known as salt-and-pepper pigmentation. Salt-and-pepper skin is characterized by vitiligo-like depigmentation, possibly triggered by trauma or immune dysfunction leading to destruction of melanocytes, with sparing of perifollicular areas. Perifollicular pigment retention has been attributed to the abundant capillary network around hair follicles, which can help preserve melanogenesis.[3]

There are several patterns of vitiligo repigmentation, the most common of which is perifollicular repigmentation.[4] Vitiligo can involve the oral mucosa and exhibit features of Koebner phenomenon. Dermoscopy findings include diffuse whitening or alteration of the pigment network and perifollicular pigmentary changes.[5]

The primary goal of treatment is to prevent progression of the disease. Because salt-and-pepper pigmentation occurs in areas of cutaneous sclerosis, hypothetically, treating the underlying sclerosis could improve the overlying dyspigmentation. Topical Janus kinase inhibitors like ruxolitinib and tofacitinib are considered when only a few cutaneous lesions are present.[6] Medications used to treat systemic sclerosis include methotrexate, mycophenolate mofetil, intravenous immunoglobulin, and biologic agents like rituximab, abatacept, and tocilizumab.[7]

Even in the absence of clinically detectable sclerosis, salt-and-pepper pigmentation can be an early indicator of systemic sclerosis and its presence should heighten suspicion for this diagnosis.

DISCLOSURES

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

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Fixed drug eruption due to ibuprofen

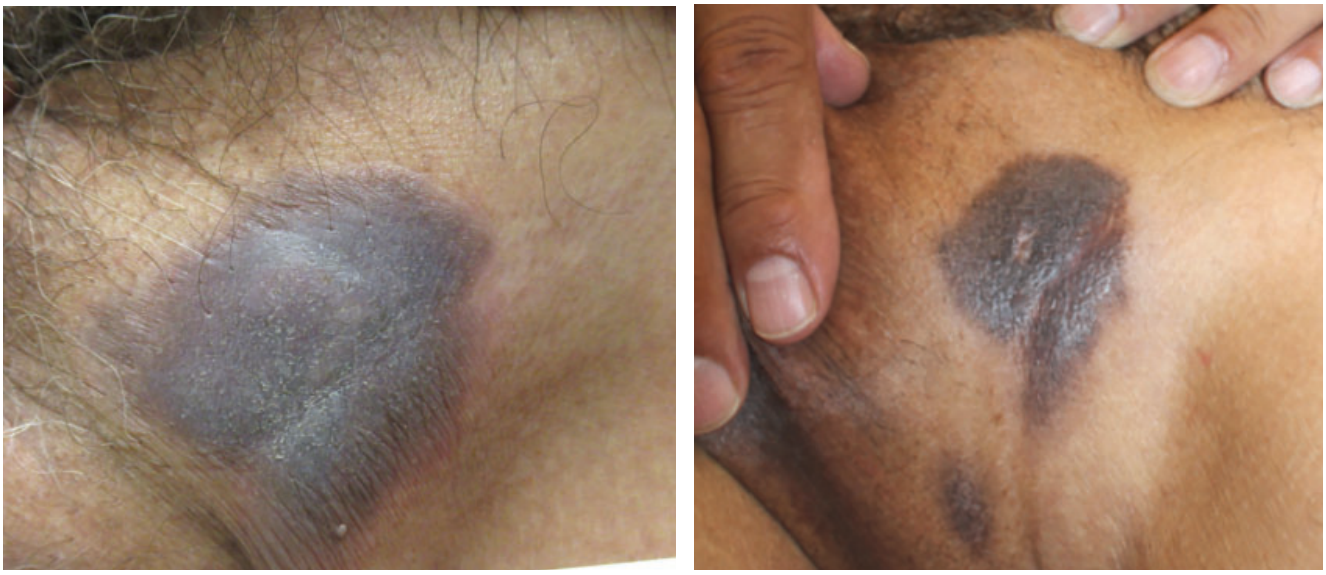

Figure 1. An 8-cm violaceous plaque with surrounding mild erythema in the patient's left inguinal fold.

A 76-year-old man with a history of lumbar radiculopathy and chronic low back pain presented with a 2-month history of a lesion on the left groin that caused a burning sensation. He had been taking 600 to 1,200 mg ibuprofen daily for back pain for more than 1 year. His other medications included gabapentin 400 mg for sleep and a daily multivitamin.

Physical examination revealed a well-demarcated violaceous 8-cm plaque with perilesional erythema on the left inguinal fold (**Figure 1**). A 4-mm punch biopsy of the skin revealed a vacuolar interface dermatitis with numerous eosinophils and melanophages. The clinical and histopathologic features combined with the patient's medication history supported a diagnosis of fixed drug eruption due to ibuprofen.

The ibuprofen was discontinued and replaced with acetaminophen. The patient was prescribed a medium-strength topical steroid for symptomatic management. The skin lesion resolved over 3 weeks and has not recurred.

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FIXED DRUG ERUPTION

The well-demarcated violaceous plaque on the groin in this patient raised suspicion for a variety of lesions, including an insect bite, bullous pemphigoid, bullous fixed drug eruption, erythema multiforme, leukocytoclastic vasculitis, lichen planus, large plaque parapsoriasis, and sarcoidosis (**Table 1**).[1,2] Of these diagnoses, the rapid onset of a solitary plaque with symptoms of burning following a recent medication exposure was most suggestive of fixed drug eruption, a relatively uncommon cutaneous reaction to medication.[3]

Fixed drug eruption lesions usually present as 1 or more circular patches with a violaceous hue on any part of the trunk or extremities. Mucosal and genital

TABLE 1
Differential diagnosis of fixed drug eruption and differentiating features

Causes	Differentiating features
Insect bite	Erythematous papule with surrounding erythema or pruritic urticarial lesion
Bullous pemphigoid	Large fluid-filled blisters on flexor surfaces
Bullous fixed drug eruption	Well-demarcated solitary erythematous or violaceous circular patches
Erythema multiforme	Recurrent papular, bullous, necrotic lesions, often with central clearing
Leukocytoclastic vasculitis	Erythematous macules with palpable purpura
Lichen planus	Pruritic violaceous papules and plaques on wrists, lower back, ankles
Large plaque parapsoriasis	Oval erythematous or hyperpigmented macules and patches with fine scales and atrophy
Fixed drug eruption	Annular oval red or violaceus patch, often with pruritus; well defined and can be blistering or erosive Clinical presentation may vary based on subtype, including mucosal, nonpigmenting, targetoid, and bullous variants Presentation may be localized or generalized
Sarcoidosis	Painless, firm, oval nodules that are flesh-colored or violaceous

Based on information from reference 2.

lesions may also occur.[3] This reaction typically recurs in the same site on reexposure to the causative medication. Although the lesions are mostly asymptomatic, there may be mild pruritus, burning, or stinging.

A history of recent medication exposures, including over-the-counter agents, is a clue to the diagnosis.[1,3] Fixed drug eruptions are associated with many drugs, especially antibiotics (eg, trimethoprim-sulfamethoxazole, tetracyclines, penicillin), nonsteroidal anti-inflammatory drugs such as ibuprofen or naproxen, antifungals, antihistamines, and acetaminophen; less common associations include carbamazepine and allopurinol.[1,3,4,5]

Workup for a suspected fixed drug eruption, including the need for laboratory evaluation and biopsy, varies based on the clinical examination and history. Because the diagnosis of fixed drug eruption is largely clinical, primary care clinicians should maintain a low threshold for referral to dermatology if there is diagnostic uncertainty or lack of supportive history.[2]

Management includes discontinuation of the drug, and the prognosis is good, with the lesion(s) usually resolving without treatment. For symptomatic relief, medium-to-high potency topical corticosteroids can be prescribed.[2] A short course of systemic corticosteroids may be needed for multiple lesions.[1]

Because these lesions are uncommon, they are often overlooked or misdiagnosed. Early diagnosis can prevent long-term complications such as rare generalized bullous lesions or postinflammatory hyperpigmentation.

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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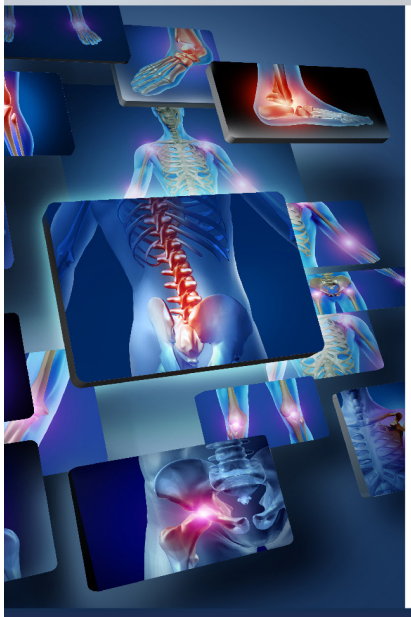

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Abdominal pain in a patient with epistaxis, telangiectasias, and arteriovenous malformations

A 53-year-old woman presented to the emergency department with 6 months of progressively worsening episodic upper abdominal pain. The pain was sharp and radiating to the back and exacerbated by eating, which caused her to avoid oral intake and led to a more than 12-kg (26.5-lb) weight loss. She also described intermittent nausea and fatigue but had no fevers, yellowing of the eyes or skin, pruritis, swelling, vomiting, diarrhea, constipation, or bloody stools. She had no history of tobacco, alcohol, or illicit drug use and had no significant travel history.

In her medical history, the patient reported recurrent epistaxis that started in adolescence, followed by the emergence of telangiectasis involving her lips, tongue, fingers, and feet during her 20s. Her epistaxis required intermittent intravenous iron infusions, but she denied a history of gastrointestinal bleeding, stroke, seizures, shortness of breath, or peripheral swelling. She had no history of migraines. Family history included hypertension and epistaxis in her mother, hypertension in her father, and epistaxis in her only sibling. Her only medication was oxymetazoline.

On examination, the patient was afebrile with a blood pressure of 109/54 mm Hg, heart rate 72 beats per minute, and oxygen saturation 98% on room air. She did not appear to be in acute distress. Extraocular movements were intact with no scleral icterus. Cardiovascular examination showed a regular rate and rhythm with no detectable murmur, rub, or gallop on auscultation. There was no jugular venous distention, parasternal heave, or peripheral edema. Breathing was unlabored and symmetric with breath sounds clear to auscultation bilaterally. The abdomen was soft, not distended, and mildly tender to palpation in the right upper quadrant, with no rebound or involuntary guarding. A negative Murphy sign was noted. There was a nontender epigastric pulsatile mass on palpation, and an abdominal bruit was identified on auscultation. Multiple pinpoint telangiectasias were present on the lips, tongue, and fingers. There were no telangiectasias of the nail beds. No jaundice of the skin was noted. Neurologic examination demonstrated intact motor and sensory function with no focal deficits.

Laboratory tests showed iron deficiency anemia (**Table 1**). Renal function tests results were within normal limts, as were alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, troponin I, and lipase. The coagulation profile was normal. No recent test results were available for comparison.

Electrocardiography demonstrated normal sinus rhythm with no prolonged intervals and no evidence of left or right atrial enlargement. Right-axis deviation (negative lead I) was present. There was no dominant R wave in lead V1 or dominant S wave in leads V5 and V6. There was normal R-wave progression, and ST-T wave abnormalities were absent.

DIFFERENTIAL DIAGNOSIS AND CHOICE OF IMAGING STUDY

1 Which imaging test is the most appropriate to obtain next?

- ☐ Computed tomography of the abdomen
- ☐ Magnetic resonance cholangiopancreatography
- ☐ Abdominal Doppler ultrasonography
- ☐ Plain radiography of the abdomen

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TABLE 1
The patient's laboratory test results during initial presentation at the emergency department

Test (reference range)	Results
Hemoglobin (12–16 g/dL)	9.0
Mean corpuscular volume (78–100 fL)	72
Red cell distribution width (11.0%–14.0%)	23.7
Platelet count (150–450 × 10^9/L)	348
Ferritin (11–307 ng/mL)	6.8
Iron (35–150 µg/dL)	20
Total iron binding capacity (225–430 µg/dL)	370
Transferrin saturation (20%–55%)	5
Aspartate aminotransferase (0–37 U/L)	15
Alanine aminotransferase (0–35 U/L)	8
Alkaline phosphatase (33–133 U/L)	126
Total bilirubin (0–1 mg/dL)	0.9
Direct bilirubin (0–0.2 mg/dL)	0.2
Thyroid-stimulating hormone (0.4–5.0 mIU/L)	2.6

The differential diagnosis of acute-on-chronic upper abdominal pain is broad. It includes the following:

- Hepatobiliary pathology (eg, symptomatic cholelithiasis, acute cholecystitis, cholangitis, hepatitis)
- Visceral organ inflammation (eg, pancreatitis, appendicitis, diverticulitis)
- Autoimmune or inflammatory conditions (eg, celiac disease, inflammatory bowel disease)
- Vascular disorders (eg, abdominal aortic aneurysm, mesenteric ischemia)
- Malignancy
- Obstruction
- Infection
- Genitourinary disorders (eg, nephrolithiasis)
- Gynecologic disorders
- Cardiac disease (eg, acute coronary syndrome)
- Functional gastrointestinal disorders.

The findings did not yet support a particular diagnosis. Her iron deficiency anemia was likely secondary to her recurrent epistaxis, which at this point had an unclear association with her acute presentation.

The presence of a palpable pulsatile abdominal mass with a bruit on auscultation initially raised suspicion for an abdominal aortic aneurysm, which would have been unusual in a woman in her 50s with no history of tobacco use or other atherosclerotic risk factors. Diagnostic mimics of abdominal aortic aneurysm include malignancy, pancreatic pseudocyst, and enlargement of the liver (particularly in cases with prominent vascularity). Otherwise, a largely benign physical examination with a nonacute abdomen and laboratory results with no readily apparent hepatobiliary injury pattern minimized concern for acute ductal impaction, visceral organ inflammation, or infection.

The appropriate initial imaging modality in this patient was abdominal Doppler ultrasonography, as it can quickly and accurately assess for the most common pathologic considerations in acute right upper quadrant pain and for abdominal aortic aneurysm.[1,2] Ultrasonography findings can often generate an actionable diagnosis. This supports its initial use over computed tomography which, although able to offer more comprehensive morphological characterization in certain disease states, is more costly and exposes the patient to ionizing radiation. Plain radiography of the abdomen would be most appropriate to evaluate for pneumoperitoneum, which was of lower concern in this patient with no predisposing factors for hollow organ perforation and no evidence of acute abdomen on physical examination. Magnetic resonance cholangiopancreatography can provide detailed information about the pancreaticobiliary ductal system, but it takes more time, is more technically difficult, and would have been premature in the initial diagnostic evaluation.

CASE CONTINUED: IMAGING RESULTS

Abdominal aortic ultrasonography revealed no aneurysm, with a maximum aortic diameter of 2.2 cm. Ultrasonography of the right upper quadrant showed no thickening of the gallbladder or gallstones, no pericholecystic fluid, and a nondilated common bile duct; Murphy sign was negative. The liver demonstrated heterogeneous echogenicity with a prominent left lobe and hepatic vascularity, including enlarged hepatic arteries and veins.

These ultrasonography findings prompted follow-up computed tomography 3-phase imaging of the abdomen and pelvis, which showed extensive arteriovenous malformations (AVMs) predominantly in the liver involving shunts from the right and left hepatic arterial branches to the hepatic portal vein (**Figure 1A**). No dissection or aneurysm of the aorta as it traversed the thorax and abdomen was noted. There was no intrahepatic ductal enlargement, and no observable extrahepatic biliary or visceral organ abnormalities were noted.

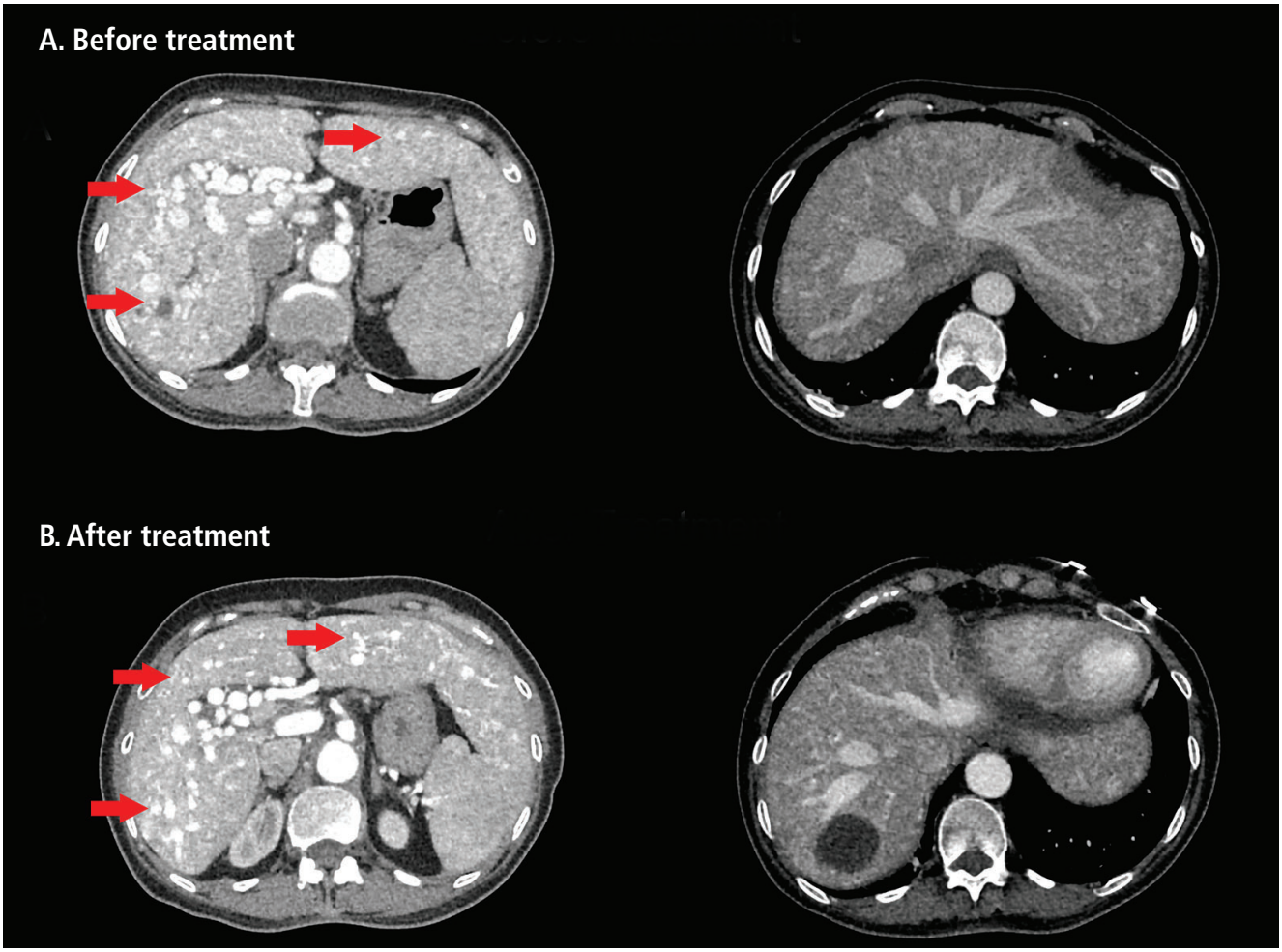

Figure 1. Computed tomography 3-phase imaging of the abdomen and pelvis showed (A) extensive arteriovenous malformations in the liver (red arrows), predominantly involving shunts from the right and left hepatic arterial branches to the hepatic portal vein. (B) Repeat computed tomography imaging of the abdomen and pelvis after 3 months of treatment with bevacizumab revealed an unchanged appearance of the liver, with extensive arteriovenous malformations (red arrows).

Computed tomography angiography of the chest showed cardiomegaly, an enlarged main pulmonary artery, and small AVMs in the bilateral lower lobes.

With no perceivable biliary compromise, the patient was treated with a proton pump inhibitor and oral analgesics, which abated her pain, and was discharged with the recommendation to follow up with her primary care physician.

DIAGNOSIS

2 What is the most likely underlying cause of this patient's epistaxis, telangiectasias, and solid-organ AVMs?

☐ Limited systemic sclerosis
☐ Ataxia-telangiectasia
☐ Generalized essential telangiectasia
☐ Hereditary hemorrhagic telangiectasia (HHT)

HHT is a rare autosomal dominant hereditary vascular disorder that leads to mucocutaneous telangiectasias and visceral AVMs.[3,4] The most well-characterized sequelae include recurrent epistaxis and solid organ bleeds. Clinical diagnosis of HHT in adults is made via the Curaçao criteria,[5] which require the presence of the following:

- Recurrent spontaneous epistaxis
- A first-degree relative with HHT
- Multiple mucocutaneous telangiectasias
- Visceral AVMs.

Fulfillment of 3 or more criteria yields a definite diagnosis.

Most patients with HHT have pathogenic variants of the *ENG*, *ACVRL1*, and *SMAD4* genes, which encode proteins of the transforming growth factor-beta superfamily (endoglin, activin A receptor-like type 1, and SMAD4, respectively).[6] Insults to this pathway result in dysregulated angiogenesis and vascular remodeling, leading to the dilated and weakened vessels that comprise telangiectasias and AVMs. Patients with pathogenic *ENG* variants have been reported to be more likely to develop pulmonary and cerebral AVMs, while those with *ACVRL1* variants have more often demonstrated hepatic involvement as well as heritable pulmonary arterial hypertension.[7,8] However, there is now less emphasis on these genotype-phenotype associations as there can be significant overlap of symptoms and organ involvement across the HHT genotypes.[8]

The presence of multiple visceral AVMs has no established pathophysiologic relationship with limited systemic sclerosis, ataxia-telangiectasia, or generalized essential telangiectasia. Limited systemic sclerosis is an autoimmune disease that may lead to telangiectasias and epistaxis; however, additional manifestations include calcinosis, Raynaud phenomenon, esophageal dysfunction, and sclerodactyly.[9] Ataxia-telangiectasia syndrome is a rare autosomal recessive neurodegenerative disease caused by a defect in the *ATM* gene, resulting in visible telangiectasias, impaired movement secondary to cerebellar defects, and variable immunodeficiencies.[10] Generalized essential telangiectasia is a rare benign condition, currently of unknown etiology, characterized by progressive onset of diffuse, symmetrical telangiectasias with no other systemic or extracutaneous manifestations.[11]

CASE CONTINUED: EVALUATION AT HHT CLINIC

One month following discharge from the emergency department, the patient presented to our HHT clinic. On evaluation, she reported a history of recurrent epistaxis and diffuse telangiectasias in her mother. Her epistaxis was described as debilitating (epistaxis severity score of 7.1), with episodes lasting longer than 15 minutes and occurring multiple times per day.[12] A colonoscopy obtained 2 months before presentation did not show gastrointestinal AVMs or polyps. She continued to experience throbbing right upper quadrant pain leading to reduced oral intake and ongoing weight loss.

Abdominal examination showed a right upper quadrant thrill and flow murmur. Laboratory results revealed worsening iron deficiency anemia. The ammonia level was 82 µmol/L (reference range ≤ 72 µmol/L) and B-type natriuretic peptide was 113 pg/mL (≤ 100 pg/mL). Electrolytes, renal function tests, and coagulation profile were normal.

A transthoracic echocardiogram with agitated saline contrast showed a left ventricle with mild hypertrophy and ejection fraction of 60% to 65%, a right ventricle with mild dilation and tricuspid annular plane systolic excursion of 32 mm (≥ 17 mm), and delayed appearance of bubbles in the left cardiac chambers suggestive of a grade 2 intrapulmonary shunt.

Right heart catheterization showed the following:

- Mean pulmonary artery pressure 28 mm Hg (≤ 20)
- Pulmonary arterial wedge pressure 10 mm Hg (≤ 15)
- Pulmonary vascular resistance 1.5 Wood units (≤ 2)
- Cardiac output 12.1 L/minute (5–6)
- Cardiac index 7.7 L/minute/m^2 (2.5–4).

There was a step-up in oxygen saturation indicating a left-to-right shunt at the level of the liver consistent with hepatic AVMs. Ventilation-perfusion lung scan did not identify areas of mismatched perfusion defects.

PULMONARY HYPERTENSION IN HHT

3 What is the interpretation of the patient's right heart catheterization findings?

- ☐ Precapillary pulmonary hypertension
- ☐ Postcapillary pulmonary hypertension
- ☐ Combined pre- and postcapillary pulmonary hypertension
- ☐ Pulmonary hypertension with a high cardiac output state

A mean pulmonary artery pressure greater than 20 mm Hg on right heart catheterization indicates the presence of pulmonary hypertension, which can be divided into precapillary, postcapillary, and unclassified causes.[13] Precapillary pulmonary hypertension is characterized by increased pulmonary vascular resistance due to pathologic remodeling and is defined as a pulmonary arterial wedge pressure of less than or equal to 15 mm Hg and pulmonary vascular resistance greater than 2 Wood units. Common causes include pulmonary arterial hypertension (eg, inherited, drug-induced, idiopathic) and chronic lung disease or hypoxia.

Pulmonary hypertension in the setting of chronic and recurrent pulmonary thromboembolism, termed *chronic pulmonary thromboembolic hypertension*, presents with precapillary pulmonary hypertension on hemody-

namics; however, this etiology would be associated with areas of mismatched perfusion defects on ventilation-perfusion lung scan.[14]

Postcapillary pulmonary hypertension is caused by increased pulmonary venous pressure and is defined as a pulmonary arterial wedge pressure greater than 15 mm Hg and pulmonary vascular resistance of 2 Wood units or less. This is most often observed in the setting of left-sided heart failure.

Combined precapillary and postcapillary pulmonary hypertension demonstrates a pulmonary arterial wedge pressure greater than 15 mm Hg and pulmonary vascular resistance greater than 2 Wood units. It can be seen in a subset of cases of left-sided heart failure in which chronically elevated filling pressures promote precapillary pulmonary remodeling, and may be associated with worse clinical outcomes.[15]

Finally, unclassified pulmonary hypertension is defined by a pulmonary arterial wedge pressure less than or equal to 15 mm Hg and pulmonary vascular resistance of 2 Wood units or less. This can be evident in cases of elevated pulmonary blood flow, such as hyperthyroidism or a high cardiac output state.

Pathophysiology of AVMs

Although patients with HHT (especially those with *ACVRL1* variants) are predisposed to heritable pulmonary hypertension, the presence of a high cardiac output state is a more common cause of pulmonary hypertension, as seen in this patient. High cardiac output in patients with HHT is a reflection of the inherent and essential pathophysiology of AVMs. Indeed, hepatic AVMs generate low-resistance vascular connections that may result in excess shunting and ischemia. Liver disease phenotypes associated with HHT include high cardiac output and portal hypertension as well as ischemic pathology like ischemic cholangiopathy and mesenteric steal syndrome. A high cardiac output state and ischemic cholangiopathy are the result of arteriovenous shunting, portal hypertension the result of arterioportal shunting, hepatic encephalopathy the result of portovenous shunting, and mesenteric artery steal syndrome the result of high-flow shunting from the right gastric artery, pancreaticoduodenal arteries, and gastroduodenal artery.[16]

In a high cardiac output state, AVMs create vascular connections that result in a high-flow state, leading to elevated pulmonary artery pressures. Chronically defective hepatic perfusion and excess neurohormonal activation can lead to progression from a high cardiac output state to high-output heart failure. This is evidenced by signs and symptoms of pulmonary and systemic congestion as well as a significant postcapillary component of pulmonary hypertension on hemodynamic assessment.[17]

Left-to-right shunting in hepatic AVMs may also result in bypassing of the peribiliary plexus, with subsequent bile duct ischemia. Chronic hypoperfusion eventually precipitates intrahepatic bile duct fibrosis with segmental dilation and strictures, resembling Caroli disease, as well as necrosis with leakage that may form a biloma.[17] Patients will present with nonspecific abdominal symptoms of biliary colic. Biochemical testing, which often demonstrates a cholestatic injury pattern, often lags behind symptom onset and does not reflect the severity of ischemic injury. However, imaging in this patient did not demonstrate observable dilations or strictures of the biliary tree to support a diagnosis of ischemic cholangiopathy.

The presence of large AVMs has been described in cases of mesenteric ischemia. The AVMs result in a steal phenomenon characterized by progressive postprandial abdominal pain and avoidance of oral intake, and may even progress to ischemic colitis.[18,19] In this patient, the sizable degree of shunting through hepatic AVMs and subsequent high-flow state also conceivably reduced perfusion of adjacent arterial beds (ie, right gastric artery, pancreaticoduodenal arteries, and gastroduodenal artery), leading to ischemic pathology and a mesenteric steal phenomenon causing chronic postprandial abdominal pain.

CASE CONTINUED: GENETIC TESTING AND TREATMENT

Genetic testing revealed a heterozygous pathogenic *ACVRL1* c.935A>C (p.His312Pro) gene variant, consistent with the patient's diagnosis of HHT. The patient received intravenous iron transfusions and was started on bevacizumab, with an induction regimen of 5 mg/kg every 2 weeks for 6 doses followed by an infusion every 4 months.

BEVACIZUMAB THERAPY

4 What is the mechanism of action of bevacizumab?

- ☐ Inhibition of vascular endothelial growth factor A
- ☐ Inhibition of fibroblast growth factor receptor
- ☐ Inhibition of platelet-derived growth factor receptor A
- ☐ Inhibition of epidermal growth factor receptor

TABLE 2
The patient's laboratory test results at time of treatment and follow-up

Test (reference range)	Results at time of therapy[a]	Results at follow-up[b]
Hemoglobin (12–16 g/dL)	7.1	10.8
Mean corpuscular volume (78–100 fL)	72	77
Red cell distribution width (11.0%–14.0%)	22.6	16.9
Platelet count (150–450 × 10^9/L)	386	293
Ferritin (11–307 ng/mL)	4.0	11.2
Iron (35–150 µg/dL)	19	28
Total iron binding capacity (225–430 µg/dL)	366	340
Transferrin saturation (20%–55%)	5	8
Aspartate aminotransferase (0–37 U/L)	20	35
Alanine aminotransferase (0–35 U/L)	11	24
Alkaline phosphatase (33–133 U/L)	149	166
Total bilirubin (0–1 mg/dL)	0.9	0.6
Direct bilirubin (0–0.2 mg/dL)	0.1	0.2
Thyroid-stimulating hormone (0.4–5.0 mIU/L)	3.015	2.8

[a]Select laboratory parameters collected on day bevacizumab therapy was started.
[b]Select laboratory parameters collected 3 months after bevacizumab therapy was started.

Bevacizumab is an inhibitor of vascular endothelial growth factor A, which impedes neoangiogenesis and promotes regression of existing dysplastic vessels.[20] Hence, its use in HHT-related liver disease may reduce the burden of arteriovenous shunting and improve hepatic perfusion. In patients with hepatic AVMs, high cardiac output refractory to salt and water restriction and diuretic therapy may be successfully treated with bevacizumab, with small controlled studies reporting improvement of symptoms and normalization of the cardiac index.[21,22] Importantly, this clinical improvement has been shown to obviate the need for liver transplantation. A study of 3 patients with HHT and ischemic cholangiopathy described improvement in abdominal pain and functional status as well as resolution of cholestatic injury with the use of bevacizumab.[23] Interestingly, patients also demonstrated radiographic evidence of clinical improvement (ie, reduction in burden of hepatic AVMs) at 1 year. Another report of 1 patient with ischemic cholangiopathy detailed a lack of clinical response to bevacizumab therapy and the onset of adverse thromboembolic events.[24]

Abdominal angina due to a mesenteric arterial steal phenomenon caused by AVMs of pancreaticoduodenal arteries in HHT has been described previously.[16] The case presented here details the presentation of a mesenteric steal phenomenon along with other hepatic phenotypes in a patient with HHT, and also represents the novel finding of a positive response to bevacizumab therapy in this setting.

CASE CONCLUSION

The patient's pulmonary AVMs were too small to coil and therefore were monitored, with no intervention. The patient underwent sclerotherapy of multiple nasal and oral telangiectasias by otorhinolaryngology. On follow-up evaluation after 3 months of bevacizumab therapy, improvement in hemoglobin levels was observed (**Table 2**). The patient reported significant reductions in epistaxis (epistaxis severity score 3.15) and abdominal pain, along with markedly improved tolerance for oral intake and an associated weight gain of 5 kg (11 lb). Additional ongoing therapy for the patient's anemia included oral ferrous sulfate (325 mg every other day); oxymetazoline was used for supplementary control of epistaxis. Notably, repeat computed tomography imaging of the abdomen and pelvis showed an unchanged appearance of the liver with an extensive AVM burden (**Figure 1B**).

Additional screening recommendations for patients with HHT include brain magnetic resonance imaging to evaluate for AVMs. Patients should also undergo a screening colonoscopy to evaluate for high-risk AVMs as well as for polyps, which have a specific association with a rare subtype of HHT caused by mutations in the *SMAD4* gene, juvenile polyposis and HHT syndrome.[25] These screening interventions did not show abnormalities in our patient.

HHT MANAGEMENT CONSIDERATIONS

This patient's chronic pain profile and clinical presentation suggested significant arteriovenous shunting, which likely resulted in progressive hypoperfusion of the mesenteric vasculature and development of the mesenteric steal syndrome. After starting bevacizumab therapy, the patient reported considerable symptomatic improvement, while radiographic evaluation revealed an unchanged burden of AVMs in the liver. This may indicate that bevacizumab produced therapeutic benefit at the level of the microvasculature that was unobservable on computed tomography imaging. The shorter follow-up duration of 3 months must also be noted. Additionally, computed tomography angiography may not adequately assess changes in the degree of the mesenteric steal effect, as it is unable to capture pre- to postprandial vessel dilation.

Iron deficiency anemia is a common complication in HHT due to frequent bleeding events, primarily in the form of epistaxis and gastrointestinal hemorrhage.[26] The resulting low blood viscosity can also exacerbate the high-flow state observed in hepatic AVMs, as well as paradoxically increase the risk for thrombotic events (eg, pulmonary embolism, cerebrovascular accidents). Treatment of epistaxis includes moisturizing topical agents, oral tranexamic acid, and ablative therapies.[3] Refractory cases are considered for management with systemic antiangiogenic treatment or more intensive surgical intervention (eg, septodermoplasty, nasal closure).

Liver transplantation is indicated in cases of HHT-related liver disease refractory to medical management.[3] This is especially relevant in such cases because alternative treatment modalities such as hepatic artery ligation or embolization are not advised because of high postprocedure mortality rates. Specifically, consideration for liver transplantation is recommended for patients with HHT who have high-output heart failure despite diuretic and antiangiogenic therapy, biliary ischemia, or severe complications of portal hypertension.[3] Patients with HHT-related liver disease are eligible for model for end-stage liver disease exception points, which can help facilitate transplantation, and 10-year posttransplant survival rates may exceed 80%.[27–29] Notably, this patient was being evaluated for liver transplantation in the setting of high cardiac output and a declining functional status. After receiving bevacizumab therapy, she had significant improvement in exercise capacity and abdominal pain. An associated weight gain effectively halted further consideration of transplantation at that time.

The presence of large pulmonary AVMs can cause significant hypoxemia, limiting patient functional status. Therefore, a multidisciplinary approach involving pulmonology, hematology, hepatogastroenterology, and otolaryngology is recommended to effectively manage this complex condition.

CONCLUSION

This patient's case highlights the physiologic impact of AVMs in patients with HHT. Depending on the size and type of connection, a high burden of arteriovenous shunting can manifest in a high cardiac output state or portal hypertension, as well as abdominal ischemic phenotypes such as ischemic cholangiopathy or mesenteric steal syndrome. Hepatic AVMs in this patient led to multiple clinical syndromes, including a high cardiac output state from arteriovenous shunting, arterioportal shunting on imaging, hyperammonemia due to portovenous shunting, and mesenteric steal syndrome. The patient had a favorable response to bevacizumab therapy. Importantly, a clinical presentation with nonspecific signs and symptoms and no immediately notable biochemical findings, as seen in this patient, may lead clinicians to conclude their investigation prematurely.

TAKE-HOME POINTS

- HHT is a rare inherited vascular disorder characterized by a positive family history, recurrent epistaxis, mucocutaneous telangiectasias, and visceral AVMs. Management involves a multidisciplinary team, ideally at an HHT Center of Excellence.
- Pulmonary hypertension is exceedingly common in this population; 2 causes related to the pathophysiology of HHT are hepatic AVM–associated high cardiac output and heritable pulmonary arterial hypertension.
- Pulmonary hypertension is categorized into precapillary, postcapillary, combined, and unclassified etiologies, depending on the pulmonary arterial wedge pressure and pulmonary vascular resistance.

- The presence of a low-resistance, high-flow AVM in the liver can generate numerous phenotypes, including high cardiac output and a mesenteric steal phenomenon; treatment of these disease entities includes bevacizumab, an inhibitor of vascular endothelial growth factor A.

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DISCLOSURES

Dr. Zumberg has disclosed teaching and speaking for the American Society of Hematology. Dr. Justice has disclosed teaching and speaking for Medtronic and consulting for Medtronic and 3D Matrix. Dr. Ataya has disclosed consulting for Savara and United Therapeutics Corporation. 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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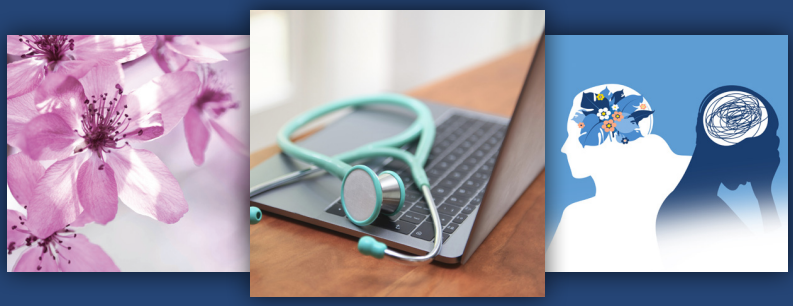

REVIEW

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Using continuous glucose monitoring data in daily clinical practice

ABSTRACT

Access to and use of glycemic data are central to optimal management of diabetes. Use of continuous glucose monitoring (CGM) data to guide the management of diabetes has increased dramatically thanks to improved ease of use, accuracy, and availability. Retrospective CGM data collected throughout the day and night allow clinicians to visualize glycemic patterns, and single-page summary views like the Ambulatory Glucose Profile (AGP) Report make rapid interpretation both feasible and intuitive. A systematic approach that integrates retrospective CGM-generated data at clinic visits and other clinical interactions with personal use of CGM data can optimize glycemic management.

KEY POINTS

- CGM is recommended for patients with type 1 diabetes and patients with type 2 diabetes treated with insulin.
- The single-page AGP Report allows for rapid and intuitive interpretation of CGM data by displaying patterns of clinically relevant hypoglycemia, hyperglycemia, and glucose variability.
- When reviewing the time-in-ranges bar, focus on increasing time in range to more than 70% and decreasing time below range to less than 4% to improve glycemia.
- Focus also on lifestyle and medication changes that make the AGP curve more flat, narrow, and in-range.

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Continuous glucose monitoring (CGM) technology, first developed in the early 2000s, has evolved to include devices with longer wear times that do not require calibration with fingerstick blood glucose monitoring, and with dramatically improved ease of use and availability.[1] In parallel with the evolution in CGM technology, there has been a dramatic increase in clinical use of CGM, both in type 1 diabetes, where CGM has become standard of care, and in insulin-treated type 2 diabetes.[2]

OVERVIEW OF CGM DEVICES

Current-generation blood glucose monitoring relies on measurement from whole blood obtained by fingerstick, while CGM technology derives glucose values from interstitial fluid via a tiny electrode inserted beneath the skin. Because diffusion of glucose from blood into the interstitial compartment is slightly delayed, interstitial glucose values are processed mathematically to improve approximation and concordance with capillary glucose levels. Although device-related delays have been minimized in recent CGM devices, typically there is a 5- to 10-minute lag between interstitial and blood glucose levels,[3] and this should be communicated to clinicians and patients.

CGM technology can be broadly divided into 2 categories: devices for personal use by patients to monitor glucose on an ongoing basis and professional devices, or clinic-owned devices used intermittently to evaluate glucose metrics and patterns at clinic visits and to guide counseling and management suggestions. Personal use has largely overshadowed professional

TABLE 1
Currently available continuous glucose monitoring systems

Type of system	Description	Examples
Real-time	Patient-owned Measures and displays data continuously (real-time) Stores data for retrospective analysis	Freestyle Libre 3 Dexcom G6 and G7, Stelo (over the counter) Guardian 3 and 4 and Simplera Eversense E3
Intermittently scanned	Patient-owned Measures glucose continuously but only displays data when swiped by a reader or smartphone Also known as "flash" glucose monitoring	Freestyle Libre 2, Rio (over the counter)
Professional	Clinic-owned system placed on patient in office Typically worn for 7–14 days Glucose data may be blinded (both systems) or unblinded (Dexcom G6 Pro) to the patient Provides data to support medication and lifestyle changes, guide shared decision-making, and identify hypoglycemia	Freestyle Libre Pro Dexcom G6 Pro

use. Professional CGM remains useful for individuals for whom personal systems are either not needed or not available and in specialized research settings. Personal CGM remains the technology of choice for most users.

Personal CGM devices can be categorized as real-time devices that measure and display glucose values continuously while worn or intermittently scanned devices (**Table 1**). The latter are somewhat simpler devices that require the user to scan a sensor worn on the body to gather glucose data. Both types of CGM devices can collect 24-hour retrospective data for evaluating patterns and glycemic metrics, and both have utility in the management of type 1 and type 2 diabetes.

EVIDENCE AND GUIDELINES ARE EVOLVING

Evidence from multiple randomized controlled trials supports the value of CGM in the management of diabetes, especially for patients who manage their diabetes with insulin.[4–9] CGM improves both hemoglobin A1c and hypoglycemia relative to fingerstick blood glucose monitoring in type 1 diabetes.[4,5] In patients with type 2 diabetes who use insulin, CGM improves hemoglobin A1c or decreases hypoglycemia to a greater degree than fingerstick blood glucose monitoring.[6–9]

Evidence-based guidelines created by specialty and advocacy groups have evolved based on this growing body of evidence. The 2024 American Diabetes Association *Standards of Medical Care in Diabetes* supports CGM for all individuals with diabetes on insulin therapy (Grade A recommendation for real-time CGM, Grade B recommendation for intermittently scanned CGM),[2] while the American Association of Clinical Endocrinology strongly recommends CGM for all patients with diabetes using basal and bolus insulin (ie, treated with both background and mealtime bolus insulin [Grade A; high strength of evidence]) and for patients with type 2 diabetes treated with less intensive insulin regimens (basal insulin only [Grade B; intermediate strength of evidence]).[10]

THE POWER OF CGM: 2 TYPES OF DATA

Medical nutrition and noninsulin and insulin therapies directly target physiologic processes to improve glucose management; CGM improves care indirectly by facilitating changes in lifestyle or diet and improving medication adherence without any direct physiologic impact. The power of CGM is in the 2 types of data it provides.

Point-in-time data: A patient with diabetes can view, on demand, a point-in-time glucose value, a trend arrow indicating whether the glucose is rising or falling, and a profile of recent glucose levels that typically represents 8 hours of data. With point-in-time data patients can see the impact of diet choices, lifestyle choices, and medications at any time, which allows real-time physiologic feedback to directly guide management of diabetes day to day.

Retrospective data: CGM technology has the capability to collect and display thousands of glucose data points retrospectively as composite glucose metrics, and

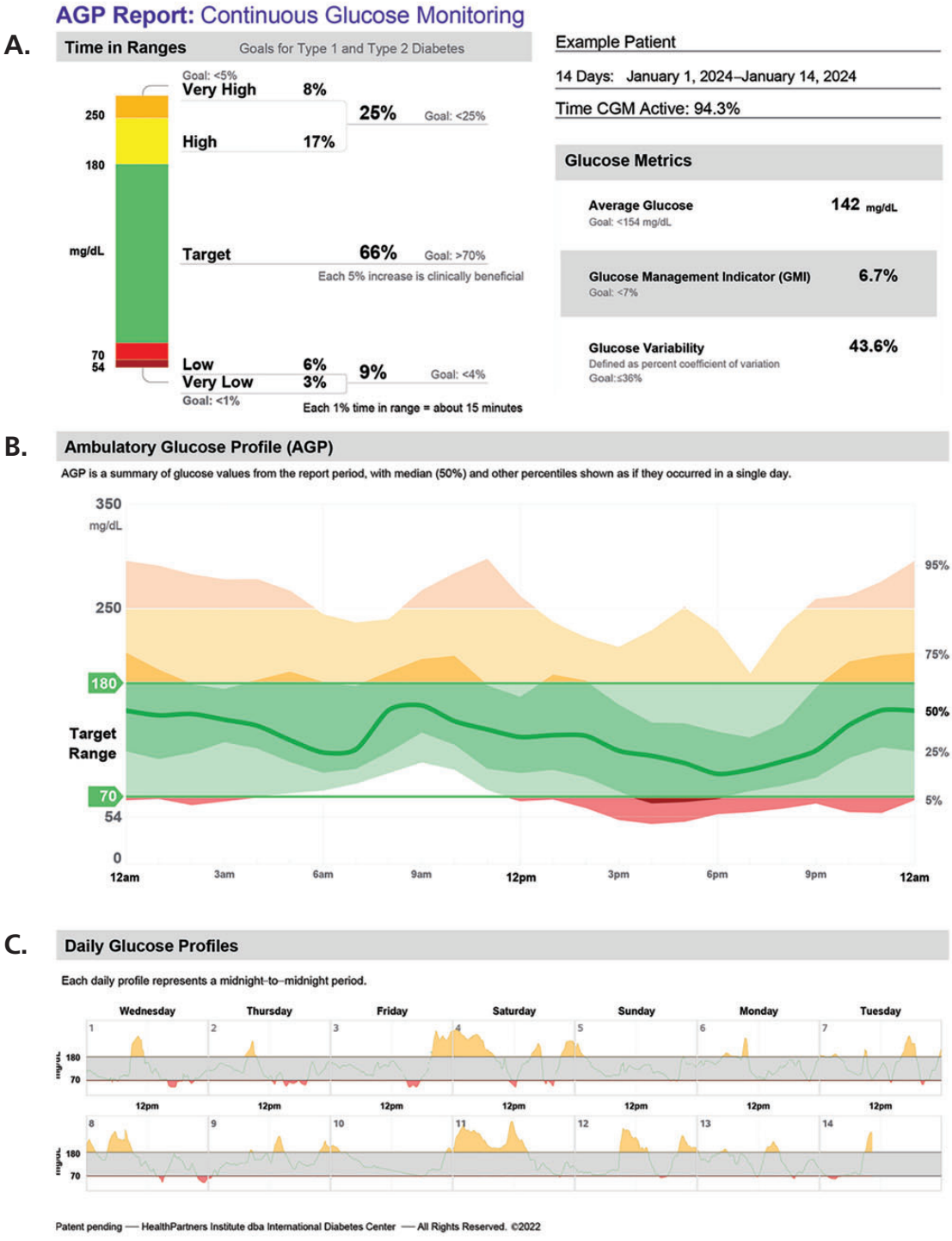

Figure 1. Example of an Ambulatory Glucose Profile Report. (A) The time-in-ranges graph quickly shows whether glycemic goals are being met and whether action is needed. Average glucose and glucose management indicator metrics provide additional information about the need to take action. Glucose variability reports variations over the course of the report period. Increased variability is a risk factor for hypoglycemia. (B) The ambulatory glucose profile curve presents a 24-hour picture of all glucose readings collected during the report period. (C) Ambulatory daily glucose profiles are thumbnails of daily values.

visually as composite and daily views for retrospective analysis.

Point-in-time and retrospective data support diabetes management in complementary ways. Retrospective data allow for shared decision-making and optimized evaluation of the safety and efficacy of glycemic management during clinical interactions. The power of retrospective CGM data lies not in the thousands of individual data points, but in composite summary reports. Just as electrocardiographic reports have evolved toward a standardized layout, presentation of CGM data has evolved toward the Ambulatory Glucose Profile (AGP), a standardized single-page summary report (**Figure 1**). Major CGM manufacturers use slight variations of the AGP Report to display data in a format that is familiar and accessible. While reports vary by manufacturer and device, AGP reports typically include the data elements described in this article.

There are several mechanisms for obtaining retrospective CGM and AGP data. CGM data from the sensor are sent to a reader or smartphone device either in real time or when the device is intermittently scanned. For intermittent scanning, the sensor should be scanned at least every 8 hours to capture all retrospective CGM data. Once transferred to a receiver or smartphone, the data can be uploaded from the device to an industry-based cloud data repository from which they can be easily viewed by the patient or, with permission (typically by an email invitation), remotely by the diabetes care team. All major CGM manufacturers have proprietary cloud-based repositories. If a clinician does not have access to a patient's cloud-based data, it is feasible in clinical settings to view retrospective data on a smartphone or reader directly. Glycemic metrics and the AGP are typically available on these devices, although the format is slightly less accessible.

THE AMBULATORY GLUCOSE PROFILE: 3 STEPS

Because CGM technology can capture glycemic data of a 24-hour day-night cycle over several weeks, CGM-derived glycemic metrics and patterns displayed in an AGP Report provide a robust picture of glycemia on both a daily and time-averaged basis. Consensus panel guidance recommends at least 14 days of CGM data with a minimum of 70% sensor wear to generate an AGP Report that enables optimal analysis and decision-making.[11] This recommendation is based on data suggesting a strong correlation between 14-day CGM metrics that measure time within recommended ranges and CGM metrics collected over longer periods of time.[12,13] The more complete the data, the more reliable the CGM metrics will be. This can be especially important when counseling people using intermittently scanned CGM technology. More frequent scanning leads to more complete data collection, with better insights into day and night patterns, frequency of hypoglycemia, and variability in glucose levels throughout the day.

Central to optimal and efficient use of CGM data is a structured approach to its evaluation. To guide decision-making, we employ a 3-step evaluation process: Determine Where to Act.

Step 1: Determine whether action is needed

Time in ranges. The upper third of the AGP Report (**Figure 1A**) provides a summary of glycemic metrics. The time-in-ranges bar graph allows rapid determination of whether glycemic goals are being met and whether action is needed to improve glucose management. The time-in-ranges graph displays:

- Percentage of time spent in prespecified glycemic ranges for the number of days included in the AGP Report—arguably the single most important measure in determining the need for action regarding the adequacy and safety of the patient's glycemic regimen
- Time *above* range, defined as the high range of 181 to 250 mg/dL and very high range greater than 250 mg/dL
- Time-*in*-range target of 70 to 180 mg/dL
- Time *below* range, in the low range of 69 to 54 mg/dL and clinically significant very low range below 54 mg/dL.

Comparison of time in range to consensus goals on the time-in-ranges graph permits the clinician or patient to decide quickly whether to act.

The patient represented in **Figure 1** has not met any of the 5 time-in-ranges goals. Action is needed because the patient has too much time below range at 9% (goal < 4%) and too much time above range at 25% (goal < 25%). Optimized glycemic management should focus on increasing time in range (70–180 mg/dL) while minimizing time below range (< 70 mg/dL). Another approach is to focus on "more green" (more time in the target range of 70 to 180 mg/dL) and "less red" (less time with a glucose level below 70 mg/dL). This is also a patient-friendly way to communicate what the goal for CGM "time in ranges" is. Time in range and time below range can be thought of together as a composite measure reflecting the adequacy of glycemic management.[14]

The goals for time above range, time in range, and time below range were chosen by the International Consensus on Time in Range (**Table 2**).[15] Time in range greater than 70% has been shown in multiple analyses to correlate loosely with a hemoglobin A1c of

about 7.0%.[16,17] A hemoglobin A1c target of 7.0% or less is supported by multiple landmark diabetes studies, including the UK Prospective Diabetes Study and the Diabetes Control and Complications Trial data.[18,19] Additionally, evidence continues to build supporting time in range itself as a key indicator of long-term complication risk.[20–25] Interest is also building for using time in range as a surrogate for hemoglobin A1c, or even as a direct glycemic measure in place of hemoglobin A1c, for purposes of quality measurement.

Time in range also provides glucose data over a much shorter timeframe than hemoglobin A1c. This frees clinicians from the traditional hemoglobin A1c–based 3-month cycle for visits, allows for more frequent changes to the diabetes regimen, and potentially reduces clinical inertia. The same international CGM consensus committee has created modified (less stringent) time-in-range goals for individuals with reduced life expectancy or significant comorbidities.[15]

Average glucose and glucose management indicator, 2 glycemic metrics on the AGP Report (**Figure 1A**), may help determine whether action is needed. The average glucose reflects values over the data collection period. The directly related glucose management indicator, expressed as a percentage, can be used clinically to estimate the hemoglobin A1c, a measure familiar to clinicians and patients.

The glucose management indicator is a calculation based on CGM-derived average glucose, and often does not align exactly with laboratory-measured hemoglobin A1c for a variety of reasons.[26] It is based purely on glycemia over the period reflected on the AGP Report and can vary from the 3-month time-averaged hemoglobin A1c due to short-term clinical impacts (eg, change in diet, use of steroids, or short-term stress). Calibration accuracy of individual sensors can impact the accuracy of glucose management indicator estimates. Additionally, the glucose management indicator is a derived value based on a linear regression equation and may not accurately correlate with laboratory hemoglobin A1c at the extremes of hemoglobin A1c values (ie, people with hemoglobin A1c in the normal range or above 10%). Conversely, laboratory-measured hemoglobin A1c can vary significantly from measures of true glycemia based on many factors impacting the life span of red blood cells.[27,28]

Variance between the glucose management indicator and hemoglobin A1c is common, expected, and often related to known factors impacting hemoglobin A1c measures. More recent data suggest that extending the data collection period for CGM metrics beyond 14 days may decrease the impact of short-term behavioral or other changes, improving the reliability of the glucose management indicator measure.[29]

TABLE 2
Glucose targets in healthy and at-risk adults

Glucose values	Target levels: Healthy nonpregnant adults	Target levels: Older and high-risk adults
Time above range		
> 250 mg/dL	< 5%	< 10%
> 180 mg/dL	< 25%	< 50%[a]
Time in range		
70–180 mg/dL	> 70%	> 50%
Time below range		
< 70 mg/dL	< 4%[b]	< 1%
< 54 mg/dL	< 1%	NA

[a]Includes values > 250 mg/dL.
[b]Includes values < 54 mg/dL.

Based on information from reference 15.

Glucose variability is a measure of variation in glucose readings at a given time of day over the course of the AGP Report period (**Figure 1A**). Increased glucose variability is an important risk factor for hypoglycemia and likely correlates with longer-term vascular risk.[30] Glucose variability is expressed on the AGP Report in terms of percent coefficient of variation. An important clinical correlate is that if the percent coefficient of variation is elevated (> 36%), the likelihood of hypoglycemia is high; by consensus, the target for glucose variability is 36% or less.[15,31] Often, high glycemic variability is associated with changes in diet, physical activity, or lack of adherence to medication, such as skipping insulin doses or taking rapid-acting insulin after the meal rather than before.

Step 2: Identify where action is needed

Evaluation of time in range allows rapid determination of whether a change in therapy is needed. Further data are needed to determine *where* the changes are needed. For that, it is necessary to review the AGP curve and the daily glucose profiles.

The AGP curve is a "modal day" view, representing all the glucose readings from the entire AGP Report period combined and presented over a single 24-hour period (**Figure 1B**). The AGP curve has a thick median line, 25% to 75% interquartile range lines (indicating

TABLE 3
Case presentation: clinical data

Demographics	
Male, age 65	
Body mass index: 42.7	
Blood pressure: 127/75 mm Hg	
Social history: single, no children, retired	
Medical history	
22-year history of type 2 diabetes	
Hypertension	
Hypercholesterolemia	
Diabetic neuropathy	
Diabetic retinopathy	
Peripheral vascular disease	
Health habits	
Nonsmoker, occasional alcohol	
No regular physical activity	
Eats 3 meals per day, often with evening snacks	
Current diabetes medications	
Metformin extended release 1,000 mg 2 times per day	
Dulaglutide 4.5 mg (maximum dose) once weekly	
Insulin glargine 60 units/day at bedtime	
Insulin lispro 10 units with meals	
Laboratory results	
Hemoglobin A1c 8.5% (reference range 4–5.6)	
Fasting blood glucose 165 mg/dL (70–99)	
Estimated glomerular filtration rate > 60 mL/minute/1.73 m^2	

where 50% of the values fall at that specific time), and 5% to 95% lines as outer boundaries. The curve allows evaluation of crucial questions:

- Is there a pattern of dangerous hypoglycemia at a certain time of day?
- Is there a postprandial pattern or hyperglycemia throughout the entire day or night or both?
- Is there excessive variability suggesting a role for modifying diet, physical activity, or medication adherence?

The AGP curve shows patterns of hypoglycemia (time below range) and hyperglycemia (time above range) that indicate quickly where action is needed.

The goal of glycemic therapy is to optimize normoglycemia while minimizing hypoglycemia. Therefore, the AGP curve can help focus therapies on interventions that reduce variability (ie, "flattening" the median line and reducing the spread of the 95% and 5% lines) while decreasing hyperglycemia and hypoglycemia by improving time in range. The goal in evaluating therapies based on the AGP curve is to move from a profile of excessive variability to a profile that is as close to normoglycemia as can be done safely. Focusing first on hypoglycemia is important in improving short-term safety; decreasing excessive variability can dramatically improve hypoglycemia risk. The focus should be on making the AGP curve flat, narrow, and in range by keeping the median line as flat as possible, the spread between the 95% and 5% lines as narrow as possible, and the whole curve in range between 70 and 180 mg/dL to the extent possible.

Daily glucose profiles provide thumbnails of daily values (**Figure 1C**). When a glycemic concern is identified on the AGP curve, daily glucose profiles facilitate further evaluation:

- Is the issue caused by a glycemic pattern observed on multiple days or a single day?
- Is there a difference on specific days of the week (eg, weekday vs weekend)?
- Is an outlying value causing the pattern in the AGP curve (a target for discussion of lifestyle and dietary issues that can impact glycemia) or an artifact?

Possible causes of artifacts in CGM data can include compression of the CGM sensor during sleep, displaced or malfunctioning sensor electrodes, or connectivity problems. Typically, artifactual CGM data, or data for which there is no rational clinical explanation, may be dismissed in evaluating the AGP Report.

Step 3: Act on the glycemic data

The AGP Report augments shared decision-making with the patient, enhancing the ability to work together to develop a plan focused on lifestyle and medication changes that address glycemic patterns identified in Step 2. Abnormal patterns can be a target for intensification or reduction in therapy; they can also suggest potential changes such as reducing carbohydrate intake or increasing physical activity to improve troublesome patterns. For safety, we address patterns of hypoglycemia first and then consider hyperglycemia patterns, either at the current or at subsequent visits, to further optimize glycemic patterns. We recommend focusing on no more than 1 or 2 glycemic patterns of concern at a time.

CASE PRESENTATION

Michael, a 65-year-old man on a regimen of basal and bolus insulin (background and mealtime bolus insulin) along with noninsulin therapies, is not meeting glycemic goals. His demographic and clinical data are outlined in **Table 3** and his glucose data in **Figure 2**.

Based on the "Determine Where to Act" guide, the first step is to review time-in-ranges metrics, with special attention to time below range. Michael's time

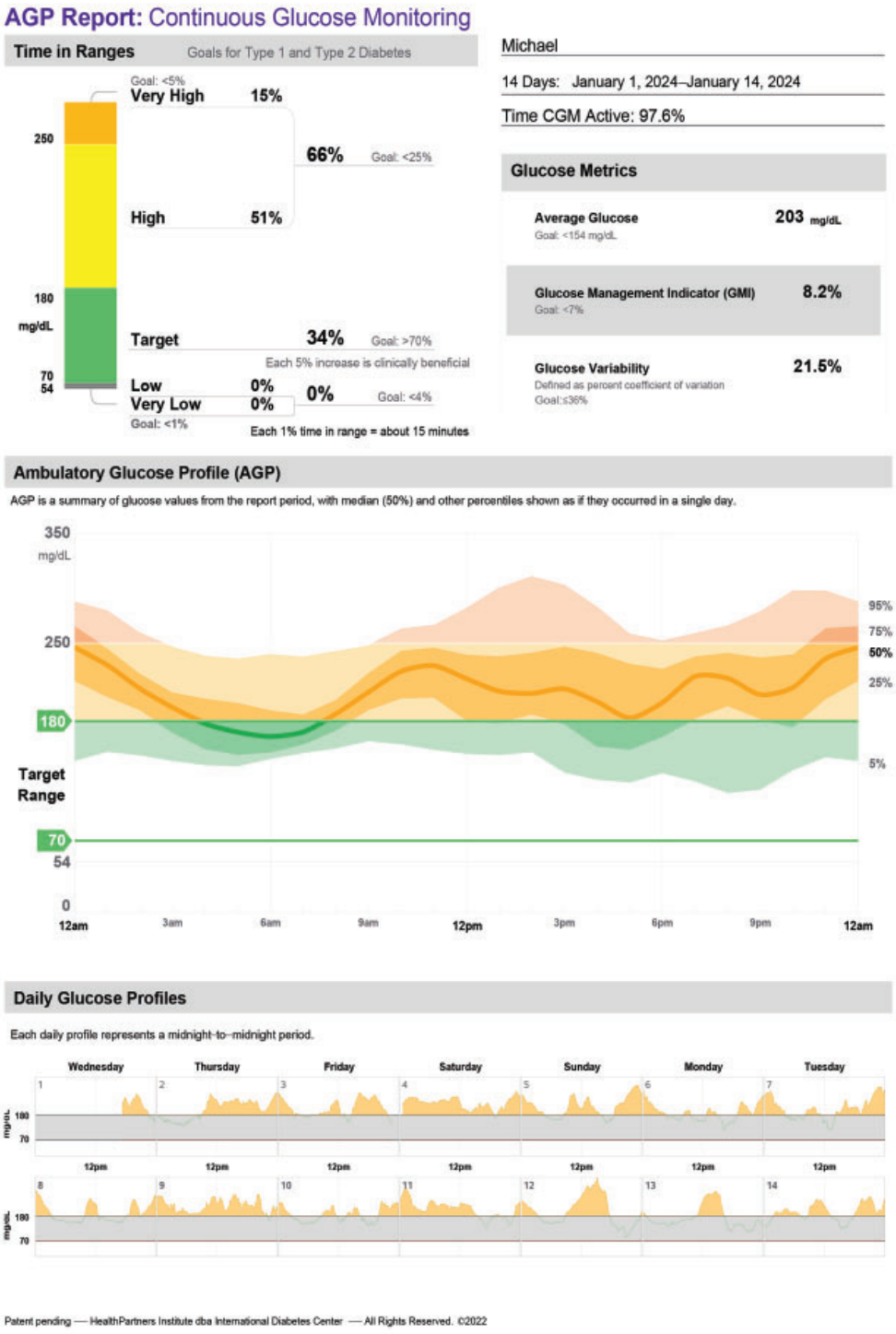

Figure 2. Patient's Ambulatory Glucose Profile Report.

TABLE 4
Coding for continuous glucose monitoring

CPT code	Description	Comments
95249	Personal (patient-owned) CGM: sensor placement, hook-up, calibration, patient training, and printout	One-time code for initial start-up and education
95250	Professional CGM (office-owned CGM), sensor placement, hook-up, calibration, patient training, removal of sensor, and printout	Billing code covers the cost of sensors and placement by clinician/staff
95251	CGM data analysis and interpretation with report by clinician	Can be billed no more frequently than every 30 days

Coding guidelines
72 hours of data are required for billing any of these codes.
-25 modifier for CGM codes can be used if billing for CGM interpretation on the same day as a Problem Visit code (99212-99215).
If a significant and separately identifiable service took place:
- 99212-99215: Pre-CGM evaluation (+) -25 95249: CGM start-up and instruction
- 99212-99215: E and M code for problem visit (+) -25 95251: CGM analysis, interpretation, and report.

CGM = continuous glucose monitoring; CPT = current procedural terminology

in range, 34%, is well below the clinical target of 70% or greater, and his time below range is 0%. We quickly determine that action is needed to improve his glycemic profile.

Step 2, "Identify where to act," requires review of the AGP curve and daily glucose profiles. Several patterns are apparent. Michael has a "stairstep" rise in glycemia during the day, corresponding with breakfast, dinner, and an evening snack. Overnight, median glucose drops from 250 mg/dL at midnight to 170 mg/dL at 6 AM. The pattern of an exaggerated overnight drop in glucose and a stairstep rise during the day suggests too much basal (background) insulin and too little bolus (mealtime bolus) insulin. Michael's average glucose of 203 mg/dL without hypoglycemia also demonstrates that the total daily dose of insulin is inadequate.

Step 3, "Act on the glycemic data," involves adjusting Michael's therapies. We address any pattern of hypoglycemia first, as that is the biggest short-term risk to patients with diabetes. Michael has no significant hypoglycemia, so our next move is to optimize insulin therapy to address hyperglycemia. Michael's insulin regimen contains an excessive amount of basal insulin relative to mealtime insulin. As a rule of thumb, the balance between basal and bolus insulin is typically 50:50 (with some individual variation in this balance).[32] This imbalance is reflected in the AGP curve, which shows a drop in glucose overnight (due to too much basal insulin), then a rise, with meals, throughout the day (due to too little mealtime insulin). A reasonable intervention would be to increase the total daily dose of insulin by 10%, then divide the total daily dose of insulin equally between basal insulin and bolus insulin. This would "rebalance" the basal and bolus insulin by redistributing the total daily dose of insulin 50:50 between basal and bolus.

With a current total daily insulin dose of 90 units (60 units of basal and 30 units of bolus insulin), we would add 10% (roughly a total daily dose of 100 units), split that between basal (50 units) and bolus (50 units) dosing, and then divide the bolus insulin between the 3 meals for a new insulin regimen of 50 units of glargine at bedtime with 16 units of lispro with meals. CGM-based management allows a more rapid cycle time. We could revisit titration in 2 weeks with a new AGP profile and continue titration until the regimen is optimized to match individual basal and bolus insulin needs.

CGM CLINICAL PEARLS

Modern CGM technology is typically straightforward and easy to use. Online videos and web-based instruction can be helpful at start-up. Additionally, care team–based resources like trained and designated staff can help ensure that data are available to clinicians at the time of clinical interactions. Building the team is a worthwhile effort to ensure success. Coding for CGM is shown in **Table 4**.

Difficulties encountered by users of CGM technology often revolve around problems with sensor adhesion or with skin irritation and dermatitis. Trimming of body hair in the area of sensor placement can be helpful, and various available skin protectants and

barriers can help both with adhesion and irritation issues. Adhesive overlays are widely available and can address adhesion issues. For patients experiencing significant challenges, local diabetes educators often have significant expertise in overcoming these challenges and can be an ideal resource.

Some commercially available CGM sensors have not been approved for use with magnetic resonance imaging, computed tomography, or radiographic technologies, and consideration should be given to removal before such testing. We recommend checking with the manufacturer's recommendation for use of CGM sensors with these technologies.

Therapeutic substances can variably interfere with glucose sensing by CGM sensors. Interference by therapeutic quantities of acetaminophen has largely been overcome, but high-dose aspirin and vitamin C can affect glucose readings, as can hydroxyurea and, for some sensors, alcohol.[33] Review of interfering substances based on CGM manufacturer recommendations is advisable.

Finally, no technology is immune from variance and errors. Neither blood glucose monitoring nor CGM technology is a "gold standard" in evaluating glucose, and variations between readings and between devices are to some degree expected. All CGM sensors are known to be less accurate in the hypoglycemia range. Concerning symptoms or discordant data may warrant confirmation with an alternate technology. Unexpected or outlying CGM data should optimally be confirmed with blood glucose monitoring if there are questions regarding the validity of data.

DISCLOSURES

Dr. Martens has disclosed consulting for Sanofi; serving as an advisor or review panel participant for Eli Lilly; teaching and speaking for Abbott Diabetes Care, Dexcom, and Eli Lilly; serving as a research principal investigator for Abbott Diabetes Care, Dexcom, and Novo Nordisk; serving as a co-principal investigator for Capillary Biomedical, Eli Lilly, Insulet Corporation, Sanofi, and Tandem Diabetes Care. Dr. Simonson has disclosed consulting for Abbott Diabetes Care and teaching and speaking for Abbott Diabetes Care and Sanofi. Dr. Bergenstal has disclosed intellectual property rights (royalties or patent sales) for Medtronic; consulting for Abbott Diabetes Care, Dexcom, Lilly, Medtronic, Novo Nordisk, and Tandem Diabetes; serving as an advisor or review panel participant for Abbott Diabetes Care, Dexcom, Lilly, Medtronic, and Novo Nordisk; serving as a research principal investigator for Abbott Diabetes Care, Insulet Corporation, Lilly, Medtronic, Novo Nordisk, and Tandem Diabetes; and serving as a research co-principal investigator for Abbott Diabetes Care, Dexcom, Insulet Corporation, Lilly, Medtronic, Novo Nordisk, and Tandem Diabetes.

The authors' employer, nonprofit HealthPartners Institute, contracts for their services and no author receives personal income for these services.

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Incidentally detected noninfectious thoracic aortitis: A clinical approach

ABSTRACT

Noninfectious aortitis is occasionally detected incidentally, either on imaging or on histopathologic review after open thoracic aortic surgery. It can present as a clinically asymptomatic, seemingly focal lesion, as diffuse inflammation throughout several aortic segments but sparing the branch vessels, or as a manifestation of a widespread systemic condition. Treatment differs based on etiology, so once identified, all patients with aortitis need a thorough evaluation, laboratory tests, complete large-vessel imaging, and a referral to a vasculitis expert. All patients with aortitis are at high risk of future vascular complications and should be followed with serial clinical evaluations and imaging.

KEY POINTS

- Noninfectious thoracic aortitis may be detected radiographically or on histopathologic review after open thoracic aortic surgery.
- Aortitis may be a manifestation of a widespread systemic illness, or a form of single-organ vasculitis, termed *isolated aortitis*.
- All patients with aortitis need a complete workup and referral to a vasculitis expert.
- Immunosuppression decisions are complex, influenced by the presence or absence of an underlying systemic condition and suspicion of persistent vasculitis, and therefore must be made on an individual basis.

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Noninfectious aortitis is occasionally detected incidentally, either on imaging or on histopathologic review after open thoracic aortic surgery. It can be a manifestation of a heterogeneous group of diseases, or in some cases, exist in isolation. Aortitis is an important finding that requires timely management because it can lead to poor outcomes such as aneurysm formation, dissection, or need for vascular surgery.

See related editorial, page 635

Below, we review how aortitis is detected, its many possible causes, and the workup and treatment of patients who are found to have it.

THE AORTA: NOT A SIMPLE TUBE

The aorta, the largest blood vessel in the body, is divided into 5 sections: the aortic root, ascending aorta, aortic arch, descending thoracic aorta, and abdominal aorta (**Figure 1**).[1] Although contiguous, aortic segments differ from one another in many important ways, including gene expression; medial wall thickness; number of smooth muscle cells, elastic fibers, and vasa vasorum; and, importantly, susceptibility to disease.[2,3] While atherosclerosis most commonly affects the abdominal aorta, noninfectious aortitis preferentially targets the thoracic segments.[3,4]

DEFINING AORTITIS: TISSUE VS IMAGING

Thoracic aortitis can be defined either histopathologically or radiographically.

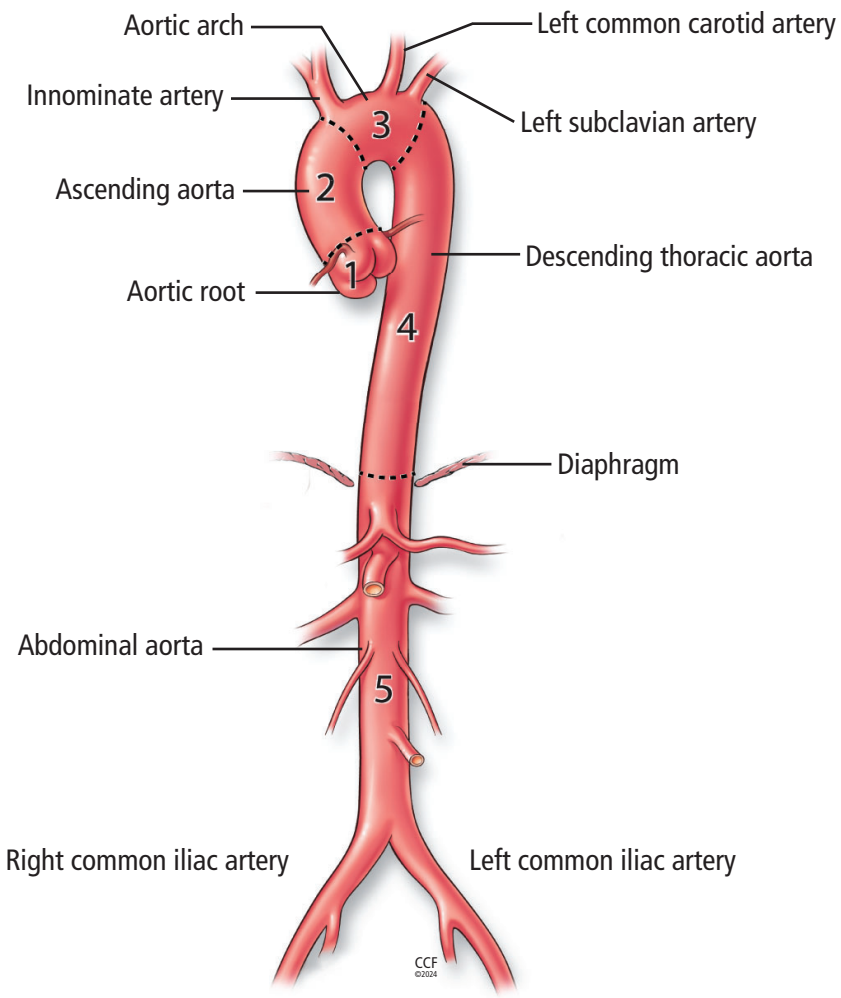

Figure 1. Anatomy of the aorta. The 5 segments of the aorta are the (1) aortic root (from the aortic valve through the sinotubular junction), (2) ascending aorta (from the sinotubular junction to the innominate artery), (3) aortic arch (from the innominate through the left subclavian artery), (4) descending thoracic aorta (left subclavian artery to the diaphragm), and (5) abdominal aorta (diaphragm to the iliac bifurcation).

Histopathologic findings

Aortitis is occasionally detected postoperatively in specimens sampled during open thoracic aortic repair.[4–8] Four patterns of tissue inflammation have been described,[9] and can provide important clues to the underlying condition:

- Granulomatous giant cell pattern, characterized by epithelioid macrophages with or without multinucleated giant cells
- Lymphoplasmacytic pattern: lymphocytes and plasma cells without a granulomatous component (staining for immunoglobulin [Ig] G4–positive plasma cells is recommended)
- Mixed inflammatory pattern: many inflammatory cell types without an overt granulomatous pattern
- Suppurative pattern: neutrophilic abscesses with necrosis (staining for microorganisms is strongly recommended).

See **Table 1**,[10–12] **Table 2**,[4–8,10–19] and **Table 3**[10–12,20–29] for the differential for these 4 patterns.

Radiographic findings

Using computed tomographic angiography (CTA) or magnetic resonance angiography (MRA), aortitis is typically defined as circumferential thickening (> 2 to 3 mm) of the aortic wall with contrast enhancement (with or without vessel wall edema in the case of MRA) without atherosclerotic plaque.[30,31] Berthod et al[32] in 2018 reported that the optimal threshold for distinguishing pathologic aortic wall thickness in patients with giant cell arteritis from controls was 2.2 mm.

TABLE 1
Infectious causes of aortitis

Diagnosis	Age at onset	Tissue pattern	Core symptoms and signs	Typical imaging features
Staphylococcus, Streptococcus, Salmonella, or *Pseudomonas* infection	Any	Suppurative	Fever, constitutional symptoms History of antecedent infection High erythrocyte sedimentation rate and C-reactive protein Positive blood cultures Positive tissue stain and culture	Usually a single lesion
Syphilis	Decades after primary infection	Lymphoplasmacytic	Possible history of untreated primary syphilis Positive syphilis serology Positive tissue stain and culture	Usually a single lesion in the thoracic aorta
Coxiella burnetii infection (Q fever)	Usually older, occurs months to years after primary infection	Granulomatous	Possible fever, abdominal pain, high C-reactive protein and erythrocyte sedimentation rate Positive immunoglobulin G Positive polymerase chain reaction of aortic tissue	More often in the abdominal than the thoracic aorta Predilection for existing aneurysms or vascular grafts
Fungal or mycobacterial infection	Any	Granulomatous (may be suppurative)	Constitutional symptoms Disseminated infection Positive tissue stain and culture	Thoracic or abdominal aorta

Based on information from references 10–12.

Aortitis shares some radiographic similarities with aortic intramural hematoma, an aortic emergency characterized by a crescent-shaped thickening of the aortic wall greater than 5 mm caused by slow bleeding and thrombus formation in the media.[1] However, the shape on CTA differs (diffuse, circumferential thickening in aortitis vs focal and crescentic thickening in aortic intramural hematoma), as does the clinical presentation. In uncertain cases in which the patient is clinically stable, positron-emission tomography with computed tomography (PET-CT) can be used to distinguish these 2 processes (in aortitis, the thickened aortic wall avidly takes up ^{18}F-fluorodeoxyglucose [FDG], but in aortic intramural hematoma it does not).[33]

Using PET-CT, FDG uptake in the aortic wall can be visually compared with uptake in the liver: if uptake is similar in both places, it is considered grade 2 (possibly indicative of aortitis), and if higher in the aorta, it is considered grade 3—compatible with aortitis.[31] As with CTA or MRA, the pattern of vascular FDG uptake is also important—aortitis produces longer, circumferential FDG-avid lesions, frequently spanning multiple sections of the aorta, while patchy or focal aortic uptake is seen in atherosclerosis.[13,31] **Figure 2** shows examples of CTA and PET-CT images of thoracic aortitis.

Can imaging detect histopathologic aortitis preoperatively?

A single study has directly compared the yield of imaging vs tissue histopathology for the diagnosis of thoracic aortitis. In 16 patients in whom histopathologic evidence of noninfectious aortitis was found following thoracic aneurysm repair, preoperative PET-CT failed to identify aortitis in 5 (31%).[34] Even in those in whom PET-CT was positive for aortitis, the preoperative C-reactive protein level was normal in 6 of the 8 in whom this laboratory result was available, indicating that neither imaging nor inflammatory markers are sufficiently sensitive to reliably identify aortitis at the tissue level.

Given that the histopathologic finding of aortitis is rare and preoperative PET-CT imaging does not identify all cases, routine preoperative PET-CT imaging in all patients undergoing thoracic aortic aneurysm repair does not seem warranted.

MANY POSSIBLE CAUSES OF AORTITIS

Aortitis can be a manifestation of numerous conditions, which range in severity from asymptomatic to life-threatening. The differential diagnosis includes infectious causes (**Table 1**), primary vasculitic diseases (**Table 2**), and secondary causes

TABLE 2
Primary vasculitic causes of aortitis

Diagnosis	Age at onset	Tissue pattern	Core symptoms and signs	Typical imaging features
Large-vessel vasculitis				
Giant cell arteritis	> 50 years	Granulomatous	Cranial or limb ischemia Constitutional symptoms High erythrocyte sedimentation rate and C-reactive protein Positive temporal artery biopsy Positive large-vessel imaging	More often in the thoracic than the abdominal aorta, and often branch vessel involvement
Takayasu arteritis	< 60 years	Granulomatous	Cranial or limb ischemia Constitutional symptoms with or without high erythrocyte sedimentation rate and C-reactive protein Positive large-vessel imaging	More often in the thoracic than the abdominal aorta, and usually branch vessel involvement
Clinically isolated aortitis	Any	Most often granulomatous, but can be any pattern	No constitutional symptoms or symptoms of systemic vasculitis or autoimmune rheumatic disease Normal C-reactive protein and erythrocyte sedimentation rate, negative serology	Most often in the thoracic aorta Can involve other segments No branch vessel involvement
Small-vessel or medium-vessel vasculitis				
Granulomatosis with polyangiitis	Any	Granulomatous, may see neutrophils and necrosis	Ear, nose, throat, lung, renal vasculitis most commonly, with or without involvement of skin, joints, nerves High erythrocyte sedimentation rate and C-reactive protein, positive antineutrophil cytoplasmic antibody, active urinalysis, positive lung and ear, nose, and throat imaging, positive tissue biopsy	Thoracic or abdominal aorta with or without branch vessels
Eosinophilic granulomatosis with polyangiitis	Any	Granulomatous, may see eosinophils	Allergic rhinitis, asthma, mononeuritis multiplex, myocarditis, skin vasculitis most commonly Peripheral eosinophilia, active urinalysis, high erythrocyte sedimentation rate and C-reactive protein, positive lung imaging Positive antineutrophil cytoplasmic antibody in 50% of cases, positive tissue biopsy	Thoracic or abdominal aorta with or without branch vessels
Behçet syndrome	Any	Mixed	Oral or genital ulcers, uveitis, pathergy High C-reactive protein Seronegative	Thoracic or abdominal aorta Pulmonary artery aneurysms

Based on information from references 4–8,10–19.

(**Table 3**). Below, we have expanded on a few of the most important noninfectious causes.

Giant cell arteritis

Giant cell arteritis is the most common primary systemic large-vessel vasculitic disease in North America, with an estimated incidence of 15 to 20 per 100,000 per year in people older than 50.[14] It classically targets the cranial arteries, including the superficial temporal arteries, facial artery, and posterior ciliary arteries, giving rise to typical symptoms of headache, scalp tenderness, jaw claudication, and vision loss. How-

TABLE 3
Secondary causes of aortitis

Diagnosis	Age at onset	Tissue pattern	Core symptoms and signs	Typical imaging features
IgG4-related disease	Any (typically older)	Lymphoplasmacytic	Lacrimal, salivary gland swelling, pancreatitis, retroperitoneal fibrosis most commonly C-reactive protein often normal Elevated serum IgG4, positive tissue IgG4	More often in the abdominal than the thoracic aorta May have periaortitis or retroperitoneal fibrosis
Rheumatoid arthritis	Any, usually long-standing rheumatoid arthritis	Granulomatous	Small joint, symmetrical polyarthritis Usually high erythrocyte sedimentation rate and C-reactive protein, positive rheumatoid factor, positive anti-cyclic citrullinated peptide Erosions on radiographs of hands and feet	Thoracic or abdominal aorta
Spondyloarthritis	Any	Lymphoplasmacytic	Inflammatory back pain Usually high erythrocyte sedimentation rate and C-reactive protein Positive human leukocyte antigen B27, positive radiographs or magnetic resonance imaging of sacroiliac joint and spine	Aortic root with or without aortic insufficiency
Systemic lupus erythematosus	Any	Lymphoplasmacytic	Photosensitivity, rash, arthritis, nephritis Positive antinuclear antibody, extractable nuclear antigen, and anti-double-stranded DNA; low complement components 3 and 4; active urine studies	Thoracic or abdominal aorta with or without branch vessels
Relapsing polychondritis	Any	Mixed	Chondritis, scleritis, tracheomalacia High C-reactive protein, seronegative	Aortic root and ascending aorta
Cogan syndrome	Any (often younger)	Mixed	Interstitial keratitis, hearing loss, vestibular dysfunction, high C-reactive protein	Ascending aorta and arch, with or without aortic insufficiency
Sarcoidosis	Any	Granulomatous (well-formed nonnecrotizing granulomas)	Lung, lymph node, musculoskeletal, hematologic, central nervous system, cardiac High C-reactive protein May have high serum or urine calcium, positive lung or cardiac imaging, positive tissue biopsy	Thoracic or abdominal aorta
Drug exposure (granulocyte-colony stimulating factor, immune checkpoint inhibitors)	Any	Unknown (usually radiographic diagnosis)	Fever, pain in back, chest, or abdomen, high C-reactive protein, relapsing polychondritis, history of exposure Resolution of imaging changes with drug withdrawal with or without prednisone	Thoracic and abdominal aorta

Ig = immunoglobulin

Based on information from references 10–12,20–29.

ever, most patients also have concomitant large-vessel involvement.[14]

In a study of 40 patients with biopsy-proven giant cell arteritis who prospectively underwent imaging, 26 (65%) had radiographic evidence of aortitis at diagnosis.[15] Conversely, about one-third of patients with aortitis detected radiographically are subsequently found to have giant cell arteritis.[35,36] The thoracic arch and descending thoracic aorta segments are most often involved, followed by the ascending and abdominal aorta.[15]

Possible red flags for aortitis in patients with giant cell arteritis are fever, inflammatory back pain, diffuse

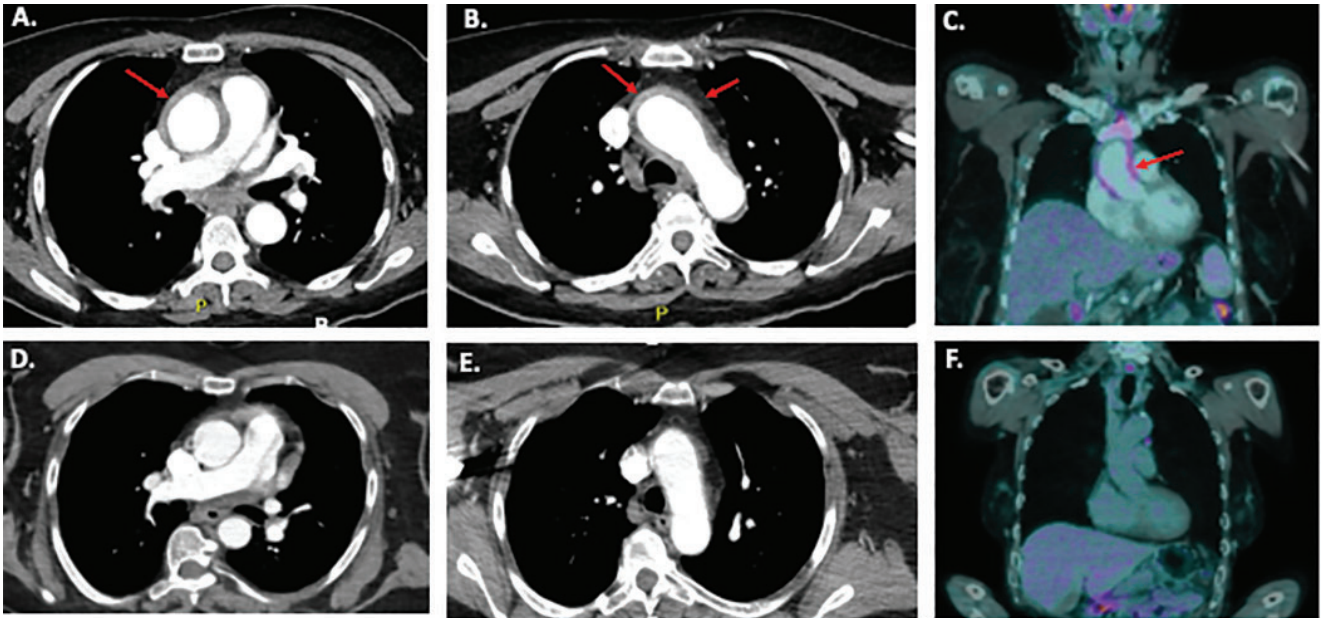

Figure 2. Imaging studies in a 55-year-old female who presented with fever, chest pain, and a C-reactive protein level of 33 mg/L (normal range < 8 mg/L). (A and B) Computed tomography angiography (CTA) of the chest and abdomen showed diffuse circumferential thickening (up to 6 mm) of the wall of the ascending aorta through the aortic arch consistent with aortitis. Red arrows indicate circumferentially thickened and FDG-avid aortic wall in the ascending aorta and aortic arch. There were no symptoms or physical signs of an underlying systemic vasculitis or autoimmune disease. Laboratory tests were normal or negative, including blood cultures, antinuclear antibody, extractable nuclear antigen, anti-double-stranded DNA, complement components 3 and 4, antineutrophil cytoplasmic antibody, serum immunoglobulin G4 level, urinalysis, interferon-gamma release assay for tuberculosis, and serology for hepatitis B and C and syphilis. (C) Positron-emission tomography with computed tomography (PET-CT) showed longitudinal grade 3 ^{18}F-fluorodeoxyglucose (FDG) uptake (ie, more than in the liver) in the ascending aorta and arch, consistent with active aortitis. Prednisone 60 mg daily was initiated, symptoms improved, and C-reactive protein level returned to normal. (D and E) CTA images of a normal ascending aorta and arch, shown for comparison. (F) PET-CT images of a normal ascending aorta without pathologic FDG uptake.

bilateral thigh pain, persistently elevated inflammatory markers, and "atypical polymyalgia rheumatica" (often defined as proximal myalgias with incomplete response to 10 to 15 mg of prednisone daily).[37] These patients may be less likely to have cranial ischemic events or vision loss.[15]

Since aortic involvement is more common than not and symptoms may be subtle or absent, all patients with giant cell arteritis should undergo imaging at baseline to look for and determine the extent of large-vessel involvement.[38] Although large-vessel vasculitis may be limited to the aorta, most patients with giant cell arteritis (23 [58%] of 40 in 1 series) also have branch vessel disease at diagnosis, most often in the brachiocephalic and subclavian arteries.[15]

Patients with giant cell arteritis should routinely undergo an assessment of peripheral pulses and bruits at each visit, and if findings are abnormal or changed they should undergo repeat vascular imaging sooner.

Takayasu arteritis

Takayasu arteritis is a rare systemic large-vessel vasculitis, with an estimated annual incidence of approximately 1 per million.[13] In contrast to giant cell arteritis, it is a disease of younger people, with typical onset between ages 15 and 40.[13,16] Aortitis is present in the majority of patients with Takayasu arteritis.[17–19] Any portion of the aorta can be affected; however, thoracic aortitis is more common in patients from North America or Europe, while abdominal aortitis more frequently occurs in those of Asian ethnicity or with childhood onset.[39]

The histopathology of Takayasu arteritis aortitis is, in many cases, indistinguishable from that of giant cell

arteritis, with granulomatous inflammation and multinucleated giant cells in the medial layer. However, significant hypertrophy of the adventitial layer, when seen, is more typical of Takayasu arteritis.[17] Ascending aortic inflammation may lead to aneurysmal change and aortic regurgitation in up to 49% of patients with Takayasu arteritis.[40]

In contrast to those with giant cell arteritis, patients with Takayasu arteritis may also develop stenoses of the aorta (either in the thoracic or abdominal portions), a radiographic finding peculiar to this form of vasculitis.[18] Coronary artery involvement, most typically due to ostial stenosis from an extension of the inflammatory process from the proximal aorta, is also a common and frequently underrecognized manifestation in these young patients.[41,42]

In addition, branch vessel stenoses are common in the carotid, proximal subclavian, mesenteric, and renal arteries and can lead to lightheadedness, headache, stroke, transient ischemic attack, extremity claudication, postprandial abdominal pain, or early-onset hypertension.[19,43] A thorough history is necessary, along with a complete cardiac and peripheral vascular examination, to detect bruits, the murmur of aortic regurgitation, asymmetry or absence of peripheral pulses, and discrepant blood pressures. Complete vascular imaging is required in all patients with suspected Takayasu arteritis for diagnosis and to document the extent of disease. Given the young age of most patients, MRA is the recommended imaging modality; however, CTA or PET-CT can also be used if needed.[44]

IgG4-related disease

In contrast to giant cell and Takayasu arteritis, IgG4-related disease is a multiorgan fibroinflammatory disease characterized by both tumefactive lesions and, potentially, aortitis. IgG4 aortitis affects about 10% of all patients with IgG4-related disease, at an average age of 58 years, and unlike giant cell arteritis, Takayasu arteritis, and clinically isolated aortitis, is more common in men.[20] IgG4-related disease may present as either a true aortitis (with radiographic aortic wall thickening or histopathologic inflammation of tissue or both), or a periaortitis (with significant perivascular inflammation but sparing the vessel wall).[21]

In 1 series, IgG4-related disease accounted for 3 (9%) of 33 cases of histopathologically identified noninfectious thoracic aortitis, and 3 of the 4 lymphoplasmacytic cases.[22] About half of patients with IgG4-aortitis have multiorgan involvement; therefore, clinical evaluation of suspected cases should aim to detect other typical sites of inflammation, such as the salivary glands, lungs, pancreas, biliary tree, and lymph nodes.[23]

Drug-induced aortitis

Aortitis can also arise after exposure to certain medications, most notably granulocyte colony–stimulating factor[25,26] and immune checkpoint inhibitors.[27,28] Most patients present with constitutional symptoms (high fever, fatigue, chills) with back, chest, or abdominal pain and significant elevation of inflammatory markers, within days (particularly for granulocyte colony-stimulating factor)[25,26] or sometimes months (immune checkpoint inhibitors)[27,28] of receiving the drug. Imaging studies are consistent with aortitis in the thoracic or abdominal aorta or both. Recognition is key, as stopping the drug is essential. In many cases, a course of prednisone is also required.[25–29]

IF ALL OTHER CAUSES ARE RULED OUT: ISOLATED AORTITIS

If infection, primary systemic vasculitides, and other rheumatic diseases are ruled out, and if the inflammation appears limited to the aorta, a diagnosis of *isolated aortitis* may be made.[45] This is a form of single-organ vasculitis in which expression is limited to the aorta, with no features of an underlying systemic vasculitis or rheumatic disease.[45] Importantly, isolated aortitis is a diagnosis of exclusion and should be considered a working diagnosis, as its natural history is incompletely understood.

It is important to distinguish whether isolated aortitis was detected histopathologically vs radiographically, as the natural history and approach to treatment may differ. Currently, no universally agreed upon nomenclature exists to distinguish these entities. Pathologists use the term *clinically isolated aortitis* to refer to aortitis identified incidentally on tissue histopathology after thoracic aortic surgery, in the absence of any identified systemic condition.[6] We follow this convention below, while the term *isolated aortitis* is used to describe aortitis detected radiographically.

Histopathologically detected isolated aortitis (clinically isolated aortitis)

In various retrospective cohort series,[4,5,7,8,45,46] noninfectious aortitis was identified histopathologically in 2.5% to 14.6% of thoracic aorta specimens taken during open surgery for aneurysm repair. Interestingly, in most of these series, clinically isolated aortitis was the most common clinical diagnosis, accounting for half to two-thirds of all cases of aortitis.[4,8,47,48]

Patients with clinically isolated aortitis can be any age, but are typically older (usually in their 60s

or 70s),[4,5,7] more are female,[4,5,7,8] and fewer have concomitant coronary artery disease than those undergoing thoracic aortic surgery for noninflammatory disease (18% vs 45%, $P < .01$).[46] Although most patients are constitutionally well, many (up to 50%) report nonspecific cardiovascular symptoms such as palpitations or dyspnea.[4] Because clinically isolated aortitis is typically recognized only postoperatively, many patients do not have blood samples sent to measure their preoperative erythrocyte sedimentation rates or C-reactive protein levels, but when these are available they are usually normal.[4,7]

Although no single histopathologic pattern defines clinically isolated aortitis, in most cases there is a granulomatous pattern indistinguishable from giant cell arteritis, with a smaller number (5% to 31%) revealing a mixed or lymphoplasmacytic infiltrate.[4,5,7]

Outcomes in patients with clinically isolated aortitis

The natural history of clinically isolated aortitis (and isolated aortitis) is hard to determine because of the retrospective nature of available data.

Comparing the outcomes of patients with clinically isolated aortitis vs those with other forms of aortitis (giant cell arteritis, Takayasu arteritis, other systemic rheumatic diseases), the risk of subsequent vascular events appears similar across groups. Although patients with clinically isolated aortitis are less likely to develop overt symptoms of vasculitis, new vascular lesions are detected radiographically in about 30% to 45% over time, and 20% to 40% require additional vascular procedures during follow-up.[4,5,49] In a series of 217 patients who underwent surgical repair of noninfectious thoracic aortitis, 5 years later 46.7% had either had a vascular complication or died, and 21.8% had undergone a second vascular procedure.[5]

Interestingly, neither the clinical diagnosis (clinically isolated aortitis vs giant cell arteritis) nor preoperative C-reactive protein level appeared to influence these outcomes, but the segment of the aorta that is involved may matter—arch aortitis was independently associated with an increased risk of vascular complications (hazard ratio [HR] 2.08, $P = .005$), while descending thoracic aortitis was independently associated with need for a second vascular procedure (HR 2.35), as was aortic dissection (HR 3.08, both P values $< .03$).[5]

Over time, 16% to 26% of patients with an initial diagnosis of clinically isolated aortitis may develop overt features of a systemic vasculitis or rheumatic disease.[4,5,45] In these cases, the most common new clinical diagnosis is giant cell arteritis/polymyalgia rheumatica, with fewer patients developing features of Takayasu arteritis, spondylarthritis, or IgG4-related disease.

Radiographically detected isolated aortitis (isolated aortitis)

Isolated aortitis is a less common clinical diagnosis in radiographic aortitis series, accounting for only 15% to 23% of all cases (giant cell arteritis is the leading diagnosis).[35,36] Although the average age in patients with isolated aortitis is similar to that in patients with clinically isolated aortitis (usually in their 60s),[35,36,50] the male-to-female ratio may be increased or even inverted compared with surgical series—9 (82%) of 11 patients were male in 1 series.[50]

Symptoms of a well-defined systemic rheumatic or vasculitic disease by definition exclude the diagnosis, but in some series up to 50% of patients with isolated aortitis had constitutional symptoms such as fever or weight loss.[50] Rather than affecting a focal segment of the thoracic aorta, in most patients the radiographic inflammation extends to multiple aortic sections, with 45% to 82% having abdominal aortitis as well.[36,50] In contrast to most surgical clinically isolated aortitis series, erythrocyte sedimentation rates and C-reactive protein values are usually significantly elevated among patients with radiographic isolated aortitis, with typical baseline values between 50 and 100 mg/L and 50 and 100 mm/hour, respectively.[35,36]

Together, these findings suggest that although patients found to have isolated aortitis based on imaging do not have extension of vasculitis outside of the aorta or clear features of a primary systemic vasculitis such as giant cell arteritis or Takayasu arteritis, they are more likely to have a clinical inflammatory syndrome (constitutional syndrome, elevated inflammatory markers) than those who are diagnosed with clinically isolated aortitis incidentally after surgery, and probably reflect a sicker population.

Outcomes in patients with isolated aortitis

In radiographic series, patients with an initial diagnosis of isolated aortitis appear more likely to have aneurysms or dissections at presentation than those with giant cell arteritis, Takayasu arteritis, or other rheumatic diseases.[35] Similarly, a study found that when followed over time, patients with isolated aortitis were significantly more likely to develop new aortic aneurysms than were patients with giant cell arteritis (6 of 44 patients vs 4 of 73 patients, $P = .009$) and more likely to require aortic surgery (16 vs 10 patients, $P = .02$) during a median of 34 months of follow-up.[36] In another study of noninfectious aortitis in which most

cases (77%) were diagnosed radiographically, isolated aortitis was an independent risk factor for subsequent vascular events or vascular procedures.[49]

Together, these studies suggest that patients with radiographically detected isolated aortitis may experience more severe aortic and vascular outcomes than those with underlying systemic vasculitis or rheumatic disease. It is unclear whether this difference is because patients with isolated aortitis have more aggressive large-vessel inflammation, or because they may come to clinical attention later or are more challenging to recognize than those with cranial or branch vessel manifestations typical of giant cell arteritis or Takayasu arteritis.

I HAVE A PATIENT WITH AORTITIS: WHAT NEXT?

See **Figure 3** for an approach to aortitis identified on either histopathology or imaging.[4–8,10–29]

History and physical examination

One should specifically look for signs and symptoms suggesting an underlying systemic process:[6,10–12]

- Infection (fever, rigors, patient acutely unwell, history of antecedent infection; **Table 1**)
- Large-vessel vasculitis (cranial, ocular, or other vascular ischemia; limb claudication; polymyalgia rheumatica; **Table 2**)
- Variable-vessel vasculitis (most typically oral, genital, ocular, or cutaneous inflammation; **Table 2**)
- Small-vessel vasculitis (ear, nose, throat, pulmonary, renal, cutaneous, or nerve involvement; **Table 2**)
- Other rheumatic diseases that may have concomitant aortic involvement, such as rheumatoid arthritis, spondyloarthritides, sarcoidosis, IgG4-related disease, Cogan syndrome, relapsing polychondritis, systemic lupus erythematosus, or other systemic autoimmune diseases (**Table 3**).

A thorough medication history is also critical to exclude drug-induced aortitis, which has been reported with granulocyte-colony stimulating factor[25,26] and immune checkpoint inhibitor exposure.[27–29]

Laboratory tests

At minimum, all patients with noninfectious aortitis should have the following laboratory tests:[10–12]

- Complete blood cell count with differential
- Serum creatinine level and urinalysis (and protein quantification if proteinuria is detected)
- Calcium level
- Albumin level
- C-reactive protein level
- Erythrocyte sedimentation rate
- Blood cultures.

Testing to exclude tuberculosis or syphilis exposure is also appropriate for most. Antinuclear antibody, antineutrophil cytoplasmic antibodies, extractable nuclear antigen, anti-double-stranded DNA, complement components 3 and 4, serum IgG4 level, or human leukocyte antigen typing (B27 or B51) may be considered.

After infection is excluded, all patients with thoracic aortitis should be referred to a vasculitis expert for assessment.

Imaging studies

Complete imaging of the entire aorta and branch vessels (skull base through thighs) at diagnosis is essential in all patients to document the extent of vascular disease already present and to serve as a baseline for comparison over time.[4] CTA, MRA, or PET-CT can be used, depending on patient factors and access.[30]

In certain conditions, PET-CT may show additional asymptomatic sites of FDG avidity outside of the aorta that may strongly suggest a particular diagnosis (eg, sinus, lung, and hilar lymph node avidity in sarcoidosis vs submandibular, lacrimal gland, and pancreatic avidity in IgG4-related disease).[21] These additional sites of activity may be safer sites to obtain confirmatory biopsy specimens in cases in which aortitis is diagnosed radiographically.

APPROACH TO TREATMENT

After aortitis is diagnosed, whether to initiate immunosuppression depends largely on the patient's clinical picture, how the aortitis was detected, and whether there is evidence or suspicion of persistent active vasculitis. For patients with a systemic vasculitic disease such as giant cell arteritis or Takayasu arteritis, immunosuppression with prednisone (with or without other agents; see "Choice of steroid-sparing therapy" below) is almost always warranted.

The benefits vs risks of systemic immunosuppression for patients with disease limited to the aorta, however, must be considered.

Treatment of clinically isolated aortitis

In surgical series, only a minority of patients with clinically isolated aortitis were treated with glucocorticoids postoperatively, and results were mixed.[4,46,51]

In 1 study, new vascular lesions were noted to develop in fewer patients with clinically isolated aortitis who received prednisone postoperatively (2 of 11, 18%) than in those who did not (27 of 54, 50%), raising a possibility of benefit.[4] In another study, of 23 patients with clinically isolated aortitis (of whom 11 received postoperative corticosteroids), the potential of harm was

Aortitis found incidentally on imaging or histopathologic study

↓

1 Screen for infection

Consider bacterial, fungal, and mycobacterial causes (**Table 1**) and obtain blood cultures

- If "suppurative" pattern: red flag for infection! Thorough testing warranted (blood culture, tissue stains, cultures, polymerase chain reaction)
- If unknown or "granulomatous" pattern: screen for tuberculosis, consider other mycobacterial, fungal, and Q fever exposures
- If unknown or "lymphoplasmacytic" pattern: screen for syphilis

If infection is excluded

↓

2 Assess for noninfectious causes

- Screen for constitutional features, polymyalgia rheumatica, or signs and symptoms of vascular ischemia that could be due to large-vessel vasculitis (giant cell arteritis or Takayasu arteritis; **Table 2**)
- Screen for symptoms and signs of other primary medium-vessel vasculitis or small-vessel vasculitis (eg, Behçet disease, antineutrophil cytoplasmic antibody–associated vasculitis; **Table 2**)
- Screen for symptoms of associated systemic autoimmune disease (eg, immunoglobulin G4–related disease, systemic lupus erythematosus, rheumatoid arthritis, spondyloarthritis, sarcoidosis, Cogan syndrome, retroperitoneal fibrosis; **Table 3**)
- Review medical history and medications

↓

3 Obtain laboratory tests

Complete blood cell count with differential, serum creatinine level, urinalysis, C-reactive protein level, erythrocyte sedimentation rate, calcium level, albumin level in all

- If "granulomatous" pattern or unknown: consider testing for antineutrophil cytoplasmic antibodies, rheumatoid factor, anti-cyclic citrullinated peptide, serum angiotensin-converting enzyme if appropriate
- If "lymphoplasmacytic" pattern or unknown: consider serum immunoglobulin G4 level, antinuclear antibody, anti-double-stranded DNA, extractable nuclear antigen panel, complement components 3 and 4, creatine kinase, human leukocyte antigen B27

↓

4 Obtain imaging of entire aorta and branch vessels for all patients to document extent of disease and presence or absence of vasculitic branch vessel disease (presence excludes isolated aortitis and clinically isolated aortitis)

↓

5 Other tests to consider

- Temporal artery biopsy or temporal artery ultrasonography (if giant cell arteritis is suspected)
- Sinus and lung imaging, other tissue biopsy (antineutrophil cytoplasmic antibody–associated vasculitis)
- Radiographs of hands and feet (rheumatoid arthritis)
- Sacroiliac joint radiographs, magnetic resonance imaging (spondyloarthritis)
- Pulmonary function tests, lung and cardiac imaging (sarcoidosis)

Figure 3. Approach to aortitis found on imaging or tissue.

Based on information from references 4–8,10–29.

raised when those receiving treatment were found to have a nonsignificantly increased growth rate of aneurysmal dilation in the descending aorta during follow-up.[51]

In the study of 217 patients with noninfectious thoracic aortitis (most with clinically isolated aortitis phenotype), no association was observed between use of postoperative glucocorticoids or other immunosuppressive treatment and vascular outcomes. Intriguingly, however, use of statins was independently associated with reduced likelihood of a subsequent vascular procedure (HR 0.47, 95% confidence interval 0.24–0.90, $P = .028$).[5] This finding deserves further study.

Ultimately, whether to initiate glucocorticoids in patients with clinically isolated aortitis identified histopathologically after surgery is controversial, and the decision often balances on whether symptoms or signs of active vascular inflammation persist, and should be made on an individual basis.

Treatment of isolated aortitis

In radiographically identified isolated aortitis, because the aortitis remains in situ, once vascular inflammation is identified, most patients require immunosuppression, regardless of clinical phenotype.[35,36,49] Due to its rapid onset of action, prednisone is typically used first-line. In some series, prednisone monotherapy was favored.[36,49] However, in view of the high risks of subsequent vascular events and the known toxicities of glucocorticoids, some authors describe early use of steroid-sparing therapy.[35]

Choice of steroid-sparing agents

Methotrexate is the most frequently used steroid-sparing agent,[35] but other options include azathioprine, mycophenolate mofetil, tocilizumab, rituximab, and leflunomide. Decisions on whether to add a steroid-sparing agent and which agent to use are influenced by the underlying cause of aortitis, as well as comorbidities and patient preference. Although there is no evidence to guide this decision in clinically isolated aortitis and isolated aortitis, in giant cell arteritis best evidence supports the early use of tocilizumab in combination with glucocorticoids, or methotrexate if tocilizumab is not available or is contraindicated.[38] Methotrexate, azathioprine, and antitumor necrosis factor alpha therapy used early in combination are excellent choices for Takayasu arteritis, while rituximab is preferred for IgG4-related aortitis when a second agent is required.[52]

Management of traditional cardiovascular risk factors

Traditional cardiovascular risk factors, including hypertension, dyslipidemia, and smoking, are common, present in one-quarter to two-thirds of patients with aortitis.[5] Due to the high risk of subsequent vascular events, blood pressure, lipid profile, blood glucose, and smoking status should be assessed in all patients. Counseling regarding lifestyle modification should be offered, and biochemical risk factors aggressively treated.[39,53]

Monitoring recommendations

Large-vessel vasculitis can progress over time, even without clinical findings or elevated inflammatory markers, both in patients with isolated aortitis or clinically isolated aortitis and those with recognized systemic large-vessel vasculitides.[4,43] Given the high frequency of new vascular lesions and need for repeat vascular procedures over time, it is advised that all patients with aortitis be monitored with serial imaging of the entire aorta and major branch vessels.[4,10,11] There is no consensus on the frequency with which imaging be repeated, but 1 center recommends it be done yearly (or sooner if clinical parameters suggest progression).[4]

SUMMARY AND RECOMMENDATIONS

Aortitis is a manifestation of a heterogenous group of diseases, so one approach does not fit all. Once it is detected, either histopathologically or radiographically, patients with aortitis require a full clinical assessment, basic laboratory tests, and complete vascular imaging of the entire aorta and major branches. These patients should be referred to a vasculitis expert to help guide the workup and determine the clinical diagnosis.

The decision to initiate immunosuppression is guided by the clinical assessment, including the presence or absence of an active systemic condition, whether active vascular inflammation persists, and the risks and benefits to the individual patient. Given the high risk of developing subsequent vascular lesions or requiring additional vascular procedures, regardless of treatment, all patients with aortitis should have aggressive management of traditional cardiovascular risk factors and be followed with serial clinical assessments, inflammatory markers, and large-vessel imaging. Team-based care may help guide treatment decisions in these complex cases.

DISCLOSURES

Dr. Clifford has disclosed serving as a research site principal investigator for Abbvie Pharmaceuticals, teaching and speaking for UCB, and serving as a research site subinvestigator for UCB.

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EDITORIAL

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Sorting out aortic aneurysms: A team enterprise

Aortic aneurysms present considerable diagnostic and treatment challenges. These difficulties relate to diverse etiologies, incomplete understanding of pathogenesis, and variations in presentation and disease course. The clinician may see this either as frustrating conundrums or fascinating opportunities for which pathways exist to provide satisfying outcomes in most cases.

See related article, page 621

NOT JUST A CONDUIT: THE PROXIMAL VS DISTAL AORTA

The differences between thoracic aortic aneurysms (TAAs) and abdominal aortic aneurysms are instructive apropos embryogenesis, vessel function, and disease vulnerability. For example, most muscular blood vessels contain smooth muscle cells derived from embryonic mesoderm. However, the proximal aorta and its proximal arch branch vessels have muscle cells derived from neuroectoderm. Modifications in embryogenesis continue caudally and within branch vessels, leading to specialization of the vascular tree to suit the organs that each aortic segment and branch vessel supplies.[1,2] Aortic wall thickness, density of vasa vasora, and elastic fiber content all diminish from proximal to more distal aortic segments.[3]

Gene expression studies have demonstrated that at least 17% of the aortic wall genome differs between the thoracic aorta and abdominal aorta.[4] In vitro studies have revealed different responses of proximal and distal aortic wall smooth muscle cells to the same stimuli (eg, transforming growth factor beta), reflecting lineage and territory-specific specialization, function, and vulnerabilities.[1] Muscular vessels are also immunologically competent organs, being equipped with dendritic cells with Toll-like receptors that are pathogen-sensing and present pathogen-associated molecules to T cells. These too differ with vessel territories.[5]

In terms of organ targeting, atherosclerosis is more common and severe as the aorta traverses the chest and abdomen, with 95% of atheromatous aneurysms located below the renal arteries.[6] Conversely, inflammatory aortic aneurysms are most common in the thoracic aorta, especially within its proximal distribution. It has long been appreciated that unique inherent properties of thoracic vs abdominal aortic walls are more critical than their location in establishing disease vulnerabilities.[7] Thus, the concept of the aorta and other vascular channels being merely conduits for blood flow is incomplete and ignores differentiation that occurred during embryogenesis and adaptation to pressure, turbulence, and organ and tissue requirements. And this story becomes still more interesting as vascular territories change their biochemical, physical, and functional properties with aging and comorbidities acquired through life's journey.[6,8]

INFLAMMATORY VS NONINFLAMMATORY ANEURYSMS

Distinctions in aorta topography become more interesting in disease context. Noninflammatory TAAs have been associated with hypertension, smoking, bicuspid aortic valves, Turner syndrome (45 monosomy X or incomplete X karyotype), and a variety of genetic anomalies affecting vessel matrix (eg, fibrillin and collagen). Many matrix disorders (eg, vascular ectatic Ehlers-Danlos, Loeys-Dietz, and Marfan syndromes) are also associated with aneurysms in the proximal aorta, as well as with other vascular and nonvascular

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anomalies and sudden death—often at a young age. Vascular and extravascular disease patterns provide useful clues to diagnosis and prognosis and inform treatment. Progression of enlargement of noninflammatory TAAs has been shown to be diminished by beta-blockers and angiotensin-receptor blockers. Risk of dissection and rupture may also be reduced by avoiding strenuous activities and trauma, especially in young patients wishing to do weightlifting and play contact sports.[9] While these prophylactic measures have proven beneficial in noninflammatory TAAs, they have not been well studied in the setting of inflammation. Nonetheless, it is reasonable, barring any contraindications, to implement interventions that reduce aortic wall pressure in patients with an inflammatory TAA.

The diagnosis of a noninflammatory TAA urges genetic testing of probands and family members. While most patients have positive family histories of similar disease features, some represent spontaneous mutations and family histories may be unrevealing. A subset of people with noninflammatory TAAs lack syndrome-associated features but nonetheless have a 20% chance of having relatives with a TAA (familial TAAs), suggesting a genetic lesion. Identifying such a patient should prompt evaluation of the thoracic aorta in first-degree relatives.[9]

It is critical for the clinician to realize that most noninflammatory TAAs enlarge slowly and are asymptomatic until they become very large. However, inflammatory and genetically determined TAAs associated with matrix anomalies may enlarge much more rapidly. In either case, symptoms such as chest or upper back pain place patients at greatly increased risk of life-threatening thoracic aorta rupture.[9]

In this issue of the *Journal*, Dr. Alison H. Clifford[10] describes a very logical approach to diagnosis and treatment of inflammatory, noninfectious thoracic aortitis. This large subset includes numerous systemic autoimmune diseases, giant cell arteritis, Takayasu arteritis, and immunoglobulin G4-related disease. If none of the foregoing can be proven and the lesion is singular and restricted to the proximal aorta, a provisional diagnosis of clinically isolated aortitis (CIA) is appropriate. It is critical to recognize that the diagnosis of CIA is always made with the proviso that CIA may be an initial presentation of a more serious multifocal or systemic illness. Such knowledge obligates periodic clinical reassessments and imaging of the entire aorta and its primary branches and inquiries that may reveal newly emerging elements of systemic diseases (eg, Takayasu arteritis, giant cell arteritis, systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, sarcoidosis, Behçet syndrome, or Cogan syndrome).[11]

TAA management requires a multispecialty team. Most rheumatologists are facile in assessment and management of the vasculitides and systemic autoimmune disorders, but cardiologists, cardiothoracic surgeons, and radiologists are essential to assess rates of TAA progression; risk of dissection, rupture, and sudden death; and timing and best type of life-saving surgical intervention. In the absence of a definite diagnosis of thoracic aortic inflammation, genetic consultation is advised to determine whether congenital matrix-associated anomalies are present.

QUESTIONS RAISED AND LESSONS LEARNED

Inflammatory TAAs raise many questions regarding pathogenesis. Studies of numerous autoimmune diseases have identified immune targets in diseases such as myasthenia gravis, Graves disease, type 1 diabetes mellitus, pemphigus, celiac disease, idiopathic membranous nephropathy, neuromyelitis optica, multiple sclerosis, and antibasement membrane (Goodpasture) disease.[12–18] At present, we do not have convincing identification of specific target autoantigens in the walls of large vessels. Molecular identity of antigens would still leave unanswered whether tissue injury occurred because of loss of tolerance to or modification of native antigen (neoantigen). Whether antigens related to recently identified aortic microbiomes play a role in pathogenesis is yet unexplored.[19–21]

We have learned a great deal about the aorta in the past 80 years. One important lesson is that calling this vessel by the same name from its origin to its terminus is misleading. Like other vessels, its characteristics are not fixed throughout its topography or over time. The aorta is an excellent example of structural and physiological adaptation to changes in physical demands and the needs of organs to be perfused. With increasingly sophisticated genetic, molecular, and immunologic research tools, it is almost certain that the fascinating questions raised in this editorial will in time be solved.

DISCLOSURES

Dr. Hoffman has disclosed being an advisor or review panel participant for Genentech.

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Treatment of *H pylori* infection

In the August 2024 issue, an error appeared in *Aldhaleei WA, Wallace MB, Harris DM, Bi Y. Helicobacter pylori: A concise review of the latest treatments against an old foe. Cleve Clin J Med 2024; 91(8):481–487. doi:10.3949/ccjm.91a.24031.* The first paragraph in the section titled "Proton pump inhibitor or potassium-competitive acid blockers" (pages 484–485 in print) should have read as follows: "The ability of *H pylori* to survive in an acidic environment necessitates the use of a proton pump inhibitor to maintain the intragastric pH above 6 and enhance the bioavailability of the antibiotics.[19,20] Several proton pump inhibitors are available, but rabeprazole or esomeprazole 20 to 40 mg twice daily is preferable. Unlike omeprazole, lansoprazole, esomeprazole, and pantoprazole, which are mainly metabolized in the liver by CYP2C19, rabeprazole is mainly metabolized by a nonenzymatic pathway and to a lesser extent by CYP2C19.[21] CYP2C19 metabolism is based on genetic predisposition (normal, intermediate, poor, rapid or ultrarapid metabolizer), resulting in more or less acid suppression, depending on the patient. Information on the type of metabolism is only available with genetic testing. Because rabeprazole metabolism is not dependent on enzyme CYP2C19 metabolism, acid suppression is more consistent and not patient-dependent.[22] Esomeprazole exhibits potent inhibition of the proton pump.[15]"

References 21 and 22 were added to the article and the subsequent references renumbered accordingly.

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The corrected article is available at www.ccjm.org.

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