Appropriateness of Excluding Pulmonary Embolism

TO THE EDITOR: I read the study by Roy and colleagues (1) with great interest. However, one thing puzzled me. In their Figure 2, the authors showed that pulmonary embolism (PE) had appropriately been ruled out when spiral computed tomography (CT) and enzyme-linked immunosorbent assay (ELISA) D-dimer results were negative in the low clinical probability group and that only a negative D-dimer result is sufficient to rule out PE in the high probability group. From basic epidemiology and studies concerning the value of D-dimer in the diagnosis of PE, we know that a negative D-dimer result provides high certainty for excluding PE (low post-test probability of PE). On the other hand, a negative D-dimer result in a group with a high a priori chance is insufficient to rule out PE (higher post-test probability of PE) (2). Could an error have occurred?

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References

IN RESPONSE: We indeed considered the exclusion of PE on the basis of a negative ELISA D-dimer result appropriate even in patients with a high pretest probability; doing so was part of the recommendations of the European Society of Cardiology (1). We acknowledge that this criterion for excluding PE is debatable from an evidence-based medicine point of view (2). It has been evaluated in large outcomes studies (3, 4), but only a few patients had the combination of a high pretest probability and a negative result on an ELISA D-dimer test (5). As a general rule, we considered as appropriate all diagnostic strategies endorsed by international experts. The low rate of recurrent PE in our study among patients excluded on the basis of these recommendations reinforces this choice. Even with such a liberal definition, only 57% of the patients underwent an appropriate diagnostic strategy; this rate was even lower when PE was excluded. Using more stringent criteria for appropriateness would have further reduced the rate of appropriate diagnostic strategies and would have reinforced our conclusion that the diagnosis of PE in clinical practice is far from optimal.

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Imatinib Mesylate in the Treatment of Refractory Idiopathic Pulmonary Arterial Hypertension

Background: Idiopathic pulmonary arterial hypertension (PAH) is a pathologic process of inappropriate vasoconstriction, vascular remodeling with smooth muscle cell hypertrophy, and in situ thrombosis, which eventually leads to right-heart failure and death. Current treatments primarily attenuate vasoconstriction and do not substantially reduce morbidity and mortality rates.

Objective: To describe a patient with severe, refractory idiopathic PAH that did not respond to conventional treatment but did show clinical and hemodynamic response to imatinib mesylate therapy, which may affect vascular remodeling.

Case Report: A 52-year-old man with rapidly progressive idiopathic PAH was evaluated for progressive dyspnea on exertion. Echocardiography and right-heart catheterization confirmed PAH; mean pulmonary artery pressure was 66 mm Hg. No cause for PAH was found. On the basis of his symptoms, the patient was categorized into World Health Organization functional class III. Therapy with furosemide and intravenous treprostinil (1) was started. Despite increases in the dose of treprostinil over the next year, his right-heart dysfunction progressed, marked volume overload developed, and his functional status deteriorated (World Health Organization class IV).

The patient was admitted for aggressive diuresis and upward titration of the treprostinil dose, but right-heart failure continued to worsen. When his condition did not respond to therapy with an intravenous treprostinil dose of 82 ng/kg of body weight per minute, the treatment was discontinued and combination therapy with intravenous epoprostenol (40 ng/kg per minute) and sildenafil (100 mg 3 times daily) (2) was begun. The epoprostenol dose was ultimately increased to 61 ng/kg per minute, but the patient’s clinical status did not improve. He required 100% high-flow oxygen, 3 inotropic agents for refractory hypotension, and continuous venovenous hemofiltration for severe volume overload. Because the patient was not considered a viable candidate for lung transplantation, compassionate treatment with imatinib mesylate (Gleevec, Novartis, East Hanover, New Jersey) was begun (3). Four weeks after imatinib...
therapy was initiated, physicians were able to discontinue treatment with all inotropic medications, sildenafil, and renal replacement, and supplemental oxygen was weaned. Subsequent right-heart catheterization revealed a 24% decrease in pulmonary vascular resistance and a 38% increase in cardiac index (Figure). A maintenance regimen of epoprostenol, furosemide, imatinib, and 5 L of supplemental oxygen was prescribed, and the patient (now World Health Organization class III) was discharged home. After 5 months of imatinib therapy, his oxygen saturation was 93% at rest while breathing room air; echocardiography showed improved right ventricular function and estimated pulmonary artery systolic pressure of 59 mm Hg.

Discussion: The dramatic clinical improvement of severe, refractory right-heart failure following the addition of imatinib to a failing regimen of approved pulmonary vasodilators in this patient suggests that imatinib may benefit others with PAH. The complex pathophysiology of PAH includes vasoconstriction, vascular wall remodeling, and in situ thrombosis. Currently, treatment of PAH relies on regimens of various pulmonary vasodilators, which demonstrate important yet limited improvements in morbidity and mortality rates. Warfarin treatment can target in situ thrombosis; however, no current therapy specifically targets vascular remodeling (4). Recent data suggest a role for the platelet-derived growth factor (PDGF) in vascular remodeling; PDGF participates in smooth muscle cell recruitment and mitogenic signaling. Levels of PDGF have been found to be higher in lung tissue from patients with PAH than in that from healthy controls. In an animal model of PAH, Schermuly and colleagues (5) recently demonstrated that imatinib, a PDGF-receptor antagonist, reversed the pathologic changes of PAH (including a decrease in right ventricular hypertrophy and pulmonary artery wall thickness) and was associated with an increased cardiac index and lower mortality rate. Subsequently, Ghofrani and colleagues (3) reported a case of a patient with refractory idiopathic PAH that did not respond to combination therapy with bosentan, iloprost, and sildenafil but demonstrated clinical improvement following initiation of imatinib therapy.

Conclusion: To our knowledge, this is only the second documented case of a clinical response to imatinib therapy in refractory idiopathic PAH and the first case in which intravenous epoprostenol was part of the failing regimen. Imatinib, a PDGF-receptor antagonist, may represent a novel therapy to target vascular remodeling in PAH. Further study of this agent in PAH is warranted.

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References
A Rare Cause of Nonalcoholic Fatty Liver Disease

Background: Nonalcoholic fatty liver disease is growing more common as the prevalence of obesity and the metabolic syndrome rises. In contrast, ichthyotic neutral lipid storage disease (NLSD) is a rare hereditary disorder that affects multiple systems. Two thirds of patients with the disease (which is also known as the Chanarin–Dorfman syndrome) have severe fatty liver disease with congenital ichthyosis, myopathy, cataracts, and neurologic disease that compromises vision and hearing.

Objective: To report a case of NLSD that was misdiagnosed as nonalcoholic fatty liver disease several years earlier.

Case Report: In August 2004, a 48-year-old man with a 4-year history of hepatic fibrosis and a 27-year history of fatty liver disease was seen in the liver transplantation outpatient clinic for a routine physical examination. Results of laboratory studies showed the following: prothrombin time, 45%; platelet count, 37 000 cells/μL; serum aspartate aminotransferase level, 99 U/L; and serum alanine aminotransferase level, 76 U/L. The patient had acute hepatitis A at the age of 8 years. Steatohepatitis was diagnosed at the age of 21 by ultrasonography and biopsy. Liver histology in 2000 showed 80% mostly microvesicular fatty degeneration with Mallory hyaline bodies, an Ishak fibrosis score of 3, and periportal and lobular hepatitis. The patient reported that he did not consume alcohol. Family history was noncontributory. Results of several series of blood tests showed normal values for hemoglobin A1c and serum cholesterol and triglycerides; serum alanine aminotransferase level, 76 U/L. The patient had acute hepatitis A at the age of 8 years. Steatohepatitis was diagnosed at the age of 21 by ultrasonography and biopsy. Liver histology in 2000 showed 80% mostly microvesicular fatty degeneration with Mallory hyaline bodies, an Ishak fibrosis score of 3, and periportal and lobular hepatitis. The patient reported that he did not consume alcohol. Family history was noncontributory. Results of several series of blood tests showed normal values for hemoglobin A1c and serum cholesterol and triglycerides; serum antinuclear antibodies were detectable, but normal γ-globulin levels suggested that autoimmune hepatitis was improbable. Ichthyosis was present since birth and was treated with salicylate therapy for many years. The patient’s liver disease was attributed to salicylate use, but histologic and biochemical abnormalities persisted after the drug was discontinued.

We suspected a more complex disease when the patient did not hear his name being called in the waiting room, suggesting undiagnosed hearing impairment. The patient reported that the impairment had been present since early childhood and had been attributed to an ear infection. Additional questioning revealed that he had been treated for cataracts, ectropion, and blepharitis. Ophthalmologic examination revealed lipid cataract and lipid deposition in the patient’s cornea. Because of this combination of findings (hearing impairment, ichthyosis, corneal lipid deposition, and fatty liver), we suspected a hereditary multisystem storage disease rather than isolated steatohepatitis with liver fibrosis. Our suspicions were further confirmed when a standard blood smear (Figure) showed lipid vacuoles in neutrophils (Jordans anomaly), which were also seen in hepatocyte nuclei of the biopsy specimen that was obtained in 2004 for grading and staging of liver disease. These findings suggested a diagnosis of NLSD, which was confirmed when genetic testing showed a mutation of the ABHD5 (CGI-58) gene.

Discussion: In 1974, Dorfman (1) reported the first known case of multisystem NLSD. Since then, most cases have been reported in Middle Eastern individuals, but the disease is believed to be underdiagnosed. Diagnosis is made simply and cost-effectively by identifying the presence of ichthyosis and lipid vacuoles in neutrophils (Jordans anomaly) in a peripheral blood smear or in other tissues (2). Although Jordans anomaly has been reported in other conditions (including familial Jordans anomaly, thalassemia, and myopathy), NLSD is likely to be the underlying defect in these cases. The presence of Jordans anomaly in the appropriate clinical context is diagnostic. The disease is associated with mutations in the ABHD5 gene on chromosome 3, which encodes a 39-kDa protein of 349 amino acids and is expressed in the skin, lymphocytes, liver, and skeletal muscle; the gene’s function is unknown (3, 4). Because the gene defect is expressed in the liver, liver transplantation may be curative.

The most common causes of steatosis and steatohepatitis are obesity, diabetes, lipid metabolism disorders, alcohol consumption, and drug toxicity. Other than NLSD, rare genetic causes of nonalcoholic fatty liver disease include genetic defects of β-oxidation (for example, deficiencies of ornithine transcarbamylase and carnitine palmitoyltransferase I and II), choline deficiency, rare mitochondrialopathies, and defects in apolipoprotein B and the microsomal triglyceride transfer protein. Distinguishing multisystem NLSD from these other causes is important because fibrogenesis in NLSD seems to be accelerated; patients with NLSD will probably experience hearing loss, cataracts, myopathy, or mental retardation. Furthermore, early diagnosis can prevent extensive diagnostic studies (including liver biopsy) that are needed for other diseases.

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References

Recurrent Iodide Mumps after Repeated Administration of Contrast Media

**Background:** Iodide mumps is an uncommon complication of intravascular administration of iodide compounds (1). The reaction arises as an acute inflammatory swelling of submandibular, sublingual, or parotid glands. In most cases, intravenous iodide should not be administered in the future to prevent more severe reactions.

**Objective:** To report the case of a patient who experienced iodide mumps 6 times after the use of 3 different forms of low-osmolar contrast media without any serious adverse event.

**Case Report:** A 60-year-old man received oral chemotherapy for 18 months for non–small-cell carcinoma of the lung. He had no history of allergy or renal dysfunction; therefore, the response to treatment was evaluated every 3 months by computed tomography of the chest with injection of iopamidol, a nonionic low-osmolar contrast agent. One day after the seventh injection of iopamidol, severe bilateral swelling occurred in the submandibular area (**Figure, left**). Palpation of the area demonstrated bilateral masses consistent with hypertrophic submandibular salivary glands. Symptoms resolved spontaneously in approximately 1 week (**Figure, right**). Computed tomography of the chest was performed 5 more times for oncologic surveillance. Iodide mumps recurred after every injection of iodide contrast agent, even when iopamidol was changed to iohexol or iopentol. Each episode was similar to the first, and no other adverse event occurred. Hyperhydration and prophylactic administration of corticosteroids and antihistamines did not prevent the recurrence of iodide mumps; the patient was also advised to try chewing gum, but this strategy was also ineffective.

**Discussion:** Iodide mumps have been reported after administration of high and low-osmolar iodide contrast media (2, 3). The mechanism of response is unclear and could be related to a toxic accumulation of iodide in salivary glands, as suggested by a high proportion of patients with renal impairment (4). No life-threatening reaction has been reported, and remission occurs spontaneously within few days. Current therapy is supportive. However, early hemodialysis may shorten the duration of swelling in patients with renal failure (2, 5).

Our report illustrates that iodide mumps is a localized, self-limited, and benign adverse event to intravascular administration of iodide compounds. The reaction is probably a class effect, because substituting 1 form of low-osmolar nonionic contrast media for another does not prevent recurrences of the condition. Of note, usual prophylactic regimens for iodide allergy are ineffective; these findings suggest that, in cases of imperative requirement (for example, percu-
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References

Correction: Which Antihypertensive Agents in Chronic Kidney Disease?
In an editorial on antihypertensive agents in chronic kidney disease (1), in the fourth sentence under the heading “ALLHAT Subgroup of Patients with Chronic Kidney Disease,” amlodipine should have been described as a dihydropyridine calcium-channel blocker, not a nondihydropyridine calcium-channel blocker.

Reference

Correction: Brief Communication: Better Ways To Question Patients about Adverse Medical Events
In an article on better ways to question patients about adverse medical events (1), the primary affiliation for Andrew L. Avins, MD, MPH, was not listed. Dr. Avins’ primary affiliation is Northern California Kaiser-Permanente Division of Research, Oakland, California.

Reference