In our study, CPAP was prescribed according to updated guidelines (2). These guidelines advise starting CPAP treatment if a patient has severe OSA or associated symptoms (mainly, excessive daytime sleepiness). All 95 women classified as having untreated severe OSA were offered CPAP. Eleven women declined, and the remaining 84 started treatment (and eventually showed bad adherence). Of the 167 women classified as having untreated mild to moderate OSA, only 47 (28.1%) began CPAP treatment (all of them had an Epworth score >10), whereas 120 (71.8%) were not offered CPAP.

In summary, 120 of 131 (91.6%) women who did not start CPAP treatment had mild to moderate OSA without excessive daytime sleepiness, whereas those who were prescribed CPAP but were nonadherent had severe or symptomatic OSA. Both groups were completely different regarding OSA severity and symptoms, so we believe that they cannot be analyzed separately. Had we only analyzed women who did not start CPAP therapy, only 11 cases with severe OSA would have been included, and the association between severe OSA and cardiovascular mortality could not have been assessed.

Francisco Campos-Rodriguez, MD
Valme Hospital
41014 Seville, Spain

Miguel A. Martinez-Garcia, MD
La Fe Hospital
46006 Valencia, Spain

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Virtual Autopsy in the Intensive Care Unit

TO THE EDITOR: The concept of a virtual autopsy as presented by Wichmann and colleagues (1) is interesting, but there are some “abnormalities” of minor clinical significance that may be detected. Figure 3 in the article is said to show a right subclavian venous catheter inadvertently placed into the neck. The image shows that the course of the right-sided catheter is totally above the clavicle, thus suggesting that it actually is a right-sided internal jugular venous catheter. That the distal tip of the catheter was placed into the cervical portion of the internal jugular vein is not surprising or particularly dangerous and should not be considered a “major finding.” Such placement can be easily detected with ultrasonography at the time of the procedure, rather than with computed tomography.

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Potential Conflicts of Interest: None disclosed.

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IN RESPONSE: We appreciate the comments from Dr. Kirsch and agree that, especially for cervical central lines, ultrasonography is an easy-to-perform, noninvasive method to control the correct positioning of the device. This case once more underscores the value of virtual and classic autopsy forms for quality control (1), because control mechanisms were not sufficient to prevent the displacement of the device. This is why we disagree with Dr. Kirsch in classifying the event as minor. In a patient with septic shock, measuring central venous pressure and providing adequate volume and vasopressor therapy are considered crucial (2). Because this cannot be assured, we classified the central venous line placed into the sigmoid sinus as a “new major finding.”

Dominic Wichmann, MD, DTM
Stefan Kluge, MD
University Medical Center Hamburg-Eppendorf
D-20246 Hamburg, Germany

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OBSERVATION

Successful Treatment of Diffuse Pulmonary Lymphangiomatosis With Bevacizumab

Background: Diffuse pulmonary lymphangiomatosis is a rare disease caused by uncontrolled proliferation of lymphatic vessels. Although histologically benign, it can lead to death. It is distinct from lymphangiectasis and lymphangioleiomyomatosis but is often misdiagnosed. Treatment options are limited and often ineffective (1, 2).

Objective: To report successful treatment of lymphangiomatosis with bevacizumab, an antibody that blocks vascular endothelial growth factor (VEGF).

Case Report: In 2005, a 40-year-old woman presented to a hospital with chest pain and fatigue, and the physicians referred her to our hospital when they found a mediastinal mass and lesions in her spleen. Surgical exploration of her mediastinum revealed an old, capsulated hematoma without active bleeding. Mediastinal biopsies found no evidence of cancer or thoracic endometriosis, and genetic and hematologic tests excluded connective tissue disease and coagulopathies. The patient had hemoptysis and hemothorax in 2006, and surgical exploration of her thorax did not provide an explanation for the bleeding. In 2008, she began to have recurrent hemoptysis, and computed tomography showed growing masses in her mediastinum, left lung, and spleen. A revised interpretation of a previous biopsy led to the diagnosis of diffuse pulmonary lymphangiomatosis 2 years later. At that time, the patient had continuous hemoptysis with anemia. Wide dissemination of lesions precluded surgical resection, and obstruction of a bronchial artery using a coil was unsuccessful. Because VEGF is known to mediate lymphatic proliferation (3, 4), we started intravenous treatment with bevacizumab, 1 mg/kg, every 3 weeks. Hemoptysis stopped, hemoglobin levels stabilized, and the tumor decreased in size (Figure, A and B). Immunohistochemical staining showed increased VEGF-A expression in diseased lymphatic vessels compared with healthy lymphatic vessels (Figure, C), despite normal plasma levels of VEGF-A (<0.1 ng/mL). After 7 treatments, bevacizumab treatment was stopped because hypertension developed. Ten months later, our patient continued without hemoptysis, and the size of the tumor was stable on computed tomography.

Discussion: Blockade of VEGF by bevacizumab turned out to be an effective treatment for diffuse pulmonary lymphangiomatosis in our patient, which is important because treatment options are limited. In 1990, a review of lymphatic disorders (2) stated that “just as the clear fluids of the lymphatics make these vessels invisible to the naked eye, so the medical knowledge and study of the lymphatic system has been nearly invisible.” During the past 2 decades, however, researchers have made considerable progress in understanding lymphatic biology, largely by identifying specific markers for lymphatic endothelium (3) and developing a better understanding of lymph vessel proliferation (that is, lymphangiogenesis). Lymphangiogenesis is mainly driven by VEGF-C and the lymph-specific receptor VEGFR-3 (3), but also by VEGF-A (4). Although therapeutic interference with VEGF-C and VEGFR-3 is still experimental, clinicians have ample experience with VEGF-A inhibition. Therefore, we treated our patient with bevacizumab, which resulted in fast reduction of tumor size and immediate clinical improvement. Another recent case report (5) suggested involvement of VEGF in lymphangiomatosis but did not provide specific evidence. Our case further supports the mediator role of VEGF-A in lymphangiomatosis by showing increased VEGF-A expression in affected lymphatic vessels (Figure, C) and tumor regression with bevacizumab (Figure, A and B).

Conclusion: This case contributes to the understanding of lymphangiomatosis by showing that VEGF-A is a mediator of lymphangiogenesis. Moreover, it indicates that some cases of pulmonary lymphangiomatosis can be effectively treated with bevacizumab; however, further clinical investigation is needed to determine its role in treating other cases of this disease.

Jurjan Aman, MD
Erik Thunnissen, MD, PhD
Marinus A. Paul, MD, PhD
Figure. Treatment and characterization of diffuse pulmonary lymphangiomatosis.

A. Treatment effects of bevacizumab on blood hemoglobin levels. Bevacizumab was given every 3 wk, indicated by asterisks.

B. The extent of lymphangiomatosis in the left lung as visualized on chest CT 1 day before (left) and 10 weeks after (right) initiation of bevacizumab treatment.

C. Immunohistochemical staining of VEGF-A in proliferative lymphatic vessels (top) vs. unaffected lymphatic vessels from the same area (bottom) (original magnification, ×5). The brown VEGF-A staining is evident in lymph endothelial cells of proliferative lymphangioma vessels (top, inset) (original magnification, ×40) but almost absent in lymph endothelial cells of the vas afferens in a lymph node (bottom, inset) (original magnification, ×40). In addition, the density of lymph endothelial cells is higher in lymphangioma vessels than in the vas afferens, suggesting proliferation of lymph endothelial cells. The lymphatic character of the proliferative vessels was confirmed by staining for VEGFR-3 (data not shown). CT = computed tomography; VEGF = vascular endothelial growth factor.

Geerten P. van Nieuw Amerongen, PhD
Anton Vonk-Noordegraaf, MD, PhD
VU University Medical Center
Amsterdam, the Netherlands

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Correction: The Increasing Burden of Mortality From Viral Hepatitis in the United States

In a recent article (1), the first sentence of the Results section of the abstract was incorrect. It should read as follows: “Between 1999 and 2007, recorded deaths from HCV increased significantly to 15 106, whereas deaths from HIV declined to 12 734 by 2007.”

This has been corrected in the online version.

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1. Ly KN, Xing J, Klevens M, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med. 2012;156:271-8. [PMID: 22351712]