James E. Loyd, M.D.
Tina V. Hartert, M.D., M.P.H.
Joshua C. Denny, M.D., M.S.
Jonathan A. Kropski, M.D.
Vanderbilt University School of Medicine
Nashville, Tennessee

References

1. Fingerlin TE, Murphy E, Zhang W, Peljto AL, Brown KK, Steele MP, Loyd JE, Cosgrove GP, Lynch D, Groshong S, *et al*. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. *Nat Genet* 2013;45:613–620.
2. Noth I, Zhang Y, Ma SF, Flores C, Barber M, Huang Y, Broderick SM, Wade MS, Hysi P, Scuirba J, *et al*. Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study. *Lancet Respir Med* 2013;1:309–317.
3. Denny JC, Ritchie MD, Basford MA, Pulley JM, Bastarache L, Brown-Gentry K, Wang D, Masys DR, Roden DM, Crawford DC. PheWAS: demonstrating the feasibility of a phenome-wide scan to discover gene-disease associations. *Bioinformatics* 2010;26: 1205–1210.
4. Denny JC, Bastarache L, Ritchie MD, Carroll RJ, Zink R, Mosley JD, Field JR, Pulley JM, Ramirez AH, Bowton E, *et al*. Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. *Nat Biotechnol* 2013;31: 1102–1110.
5. Claar D, Larkin EK, Bastarache L, Blackwell TS, Loyd JE, Denny JC, Kropski JA. A Phenome-Wide-Association Study (PheWAS) identifies common genetic risk among clinical risk factors for idiopathic pulmonary fibrosis (IPF) [abstract]. *Am J Crit Care Med* 2015;191: A2204.
6. Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, von Mutius E, Farrall M, Lathrop M, Cookson WO; GABRIEL Consortium. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010;363:1211–1221.
7. Bønnelykke K, Sleiman P, Nielsen K, Kreiner-Møller E, Mercader JM, Belgrave D, den Dekker HT, Husby A, Sevelsted A, Faura-Tellez G, *et al*. A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations. *Nat Genet* 2014;46:51–55.
8. Albrecht E, Sillanpää E, Karrasch S, Alves AC, Codd V, Hovatta I, Buxton JL, Nelson CP, Broer L, Hägg S, *et al*. Telomere length in circulating leukocytes is associated with lung function and disease. *Eur Respir J* 2014;43:983–992.
9. Belsky DW, Shalev I, Sears MR, Hancox RJ, Lee Harrington H, Houts R, Moffitt TE, Sugden K, Williams B, Poulton R, *et al*. Is chronic asthma associated with shorter leukocyte telomere length at midlife? *Am J Respir Crit Care Med* 2014;190:384–391.

Coronavirus NL63-induced Adult Respiratory Distress Syndrome

To the Editor:

Coronaviruses are positive RNA-enveloped viruses. The first two human coronaviruses, HCoV-229E and HCoV-OC43, were discovered in the mid-1960s. They are a well-known cause of the common cold (1). The world epidemic of severe acute respiratory syndrome human coronavirus (SARS-HCoV) in 2002–2003 reintroduced the Coronaviridae family. In 2004 and 2005, respectively, two new coronaviruses were discovered: NL63 and HKU1 (2, 3). The Coronaviridae family is further subclassified into two genera: the alpha coronaviruses (HCoV-229E and HCoV-NL63) and beta coronaviruses (HCoV-HKU1, HCoV-OC43, Middle East respiratory syndrome [MERS]-HCoV, and SARS-HCoV). HCoV-NL63 infection causes mostly upper and at times lower respiratory tract infection, community-acquired pneumonia, and also croup in children (4). In 2012, another coronavirus-related epidemic occurred, this time in the Middle East, which led to the identification of the MERS-HCoV (5).

A 76-year-old woman was admitted because she had experienced 4 days of low-grade fever, dyspnea, and malaise. She had no discernible comorbidities and took no medications. Ceftriaxone and azithromycin were initiated, but shortly after admission, her respiratory failure worsened, requiring mechanical ventilation. Her Pa_{O_2}/Fi_{O_2} ratio was 70, consistent with severe adult respiratory syndrome (ARDS), which remained her only failing system throughout her entire course. She was turned prone, and inhaled nitric oxide was added.

Chest roentgenogram revealed bilateral pulmonary infiltrates, and echocardiogram showed normal biventricular function. White blood cell count was normal. Blood, urine, and respiratory secretion cultures were all sterile. Serology for HIV was negative. Polymerase chain reaction (PCR) for cytomegalovirus from both blood and bronchoalveolar lavage (BAL) was negative. PCR from oral swab and nasal wash were negative for influenza species, human respiratory syncytial virus, and para-influenza viruses but were positive for coronavirus NL63. PCR from BAL was positive for HCoV-NL63 as well (cell count and differential were not performed). The presence of the virus was confirmed in consecutive samples from the nasal and oral cavities, revealing a persistent increase in viral load (Figure 1). BAL fluid was sterile for bacteria and for *Pneumocystis jirovecii*. PCRs from BAL fluid for SARS-HCoV and MERS-HCoV were negative. Because of the rarity of coronavirus-induced ARDS, a search for occult malignancy or immune deficiency revealed normal bone marrow biopsy, immunoglobulins, and abdominal ultrasound.

The persistently positive PCR for HCoV-NL63 in both upper and lower respiratory tract secretions, and the increase in viral load, as well as a negative extensive search for an alternative etiology, strongly suggest that HCoV-NL63 was indeed the cause of her fatal illness. After 27 days of nonresolving severe ARDS, she died as a result of hospital-acquired sepsis and multiorgan failure. A postmortem exam was not performed.

In 2010, a case of fatal HCoV-NL63 pulmonary infection during the late-engraftment phase was reported (6). An Australian study reported that 2% of patients presenting to the hospital because of respiratory symptoms tested positive for HCoV-NL63, and 81% of these patients were diagnosed with lower respiratory tract disease; all of them required admission to the hospital, 56% had an abnormal chest roentgenogram, and one immunocompromised patient died, yet none of these patients had ARDS (7).

Acute interstitial pneumonitis (AIP), an idiopathic form of acute lung injury first described by Hamman and Rich in 1935 (8), is a rapidly progressive disease frequently leading to respiratory failure and mechanical ventilation and is associated with very poor

Author Contributions: O.G., Y.S.A., and Y.A. have drafted and revised the manuscript, and O.G., L.F., O.A.F., and Y.A. have treated the patient, collected the data, and reviewed the literature.

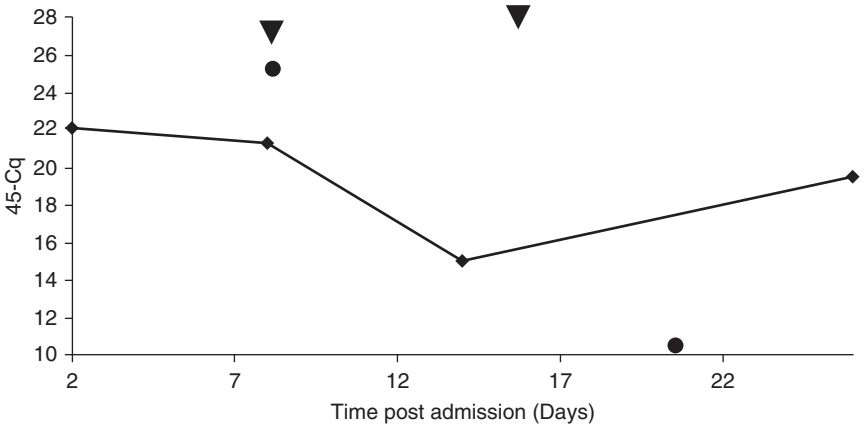

Figure 1. Relative quantification of coronavirus NL-63 by multiplex hydrolysis probes-based real-time polymerase chain reaction. The raw nasopharyngeal washing matter, or bronchoalveolar lavage, or swabs were added to a test tube containing 1.0 ml RPMI solution that was vortexed. Nucleic acid extraction was performed using NucliSense EasyMag (Biomerieux, Marcy l'Etoile, France). Four hundred microliters of aspirate was extracted into 50 μl elution solution. A set of primers and probes was used to detect four coronaviruses (229E, HKU1, OC43, and NL63), along with an internal control set, by multiplex hydrolysis probes-based real-time polymerase chain reaction. The relative expression of coronavirus RNA transcripts for each day tested is conveyed in 45 quantitation cycle values (after correction to the quantitation cycle value of the internal control). *Diamonds* represent swabs; *circles* represent nasal wash, and *triangles* represent bronchoalveolar lavage.

prognosis. The histopathologic appearance in AIP is of diffuse alveolar damage characterized by three phases: acute exudative, organizing proliferative, and fibrotic. It should be emphasized that AIP cannot be distinguished from ARDS on the basis of histology alone (because of the patient's clinical condition, a lung biopsy was not done). This distinction can be ascertained only when there is no identifiable alternative etiology after a thorough clinical evaluation (9). The patient under discussion could have been easily diagnosed as another case of AIP, had PCR for HCoV-NL63 not been performed. As we previously suggested, it is possible that AIP is an entity encompassing a wide variety of etiologies that are often unidentified, some of which may be viral in origin (10). This understanding, as well as our ever-improving diagnostic abilities in identifying viral pathogens, may have important implications on clinical practice. When clinically appropriate, a thorough search for viral etiology should be a part of the diagnostic workup of these patients, as it may obviate invasive procedures (biopsies) and potentially harmful therapeutic interventions such as broad-spectrum antibiotics, corticosteroids, and cytotoxic agents. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Ori Galante, M.D.
Yonat Shemer Avni, Ph.D.
Lior Fuchs, M.D.
Ofira Azulay Ferster, M.D.
Yaniv Almog, M.D.
Ben Gurion University of the Negev
Beer-Sheva, Israel

References

1. Geller C, Varbanov M, Duval RE. Human coronaviruses: insights into environmental resistance and its influence on the development of new antiseptic strategies. *Viruses* 2012;4:3044–3068.
2. van der Hoek L, Pyrc K, Jebbink MF, Vermeulen-Oost W, Berkhout RJ, Wolthers KC, Wertheim-van Dillen PM, Kaandorp J, Spaargaren J, Berkhout B. Identification of a new human coronavirus. *Nat Med* 2004;10:368–373.
3. Woo PC, Lau SK, Chu CM, Chan KH, Tsoi HW, Huang Y, Wong BH, Poon RW, Cai JJ, Luk WK, *et al*. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. *J Virol* 2005;79:884–895.
4. van der Hoek L, Sure K, Ihorst G, Stang A, Pyrc K, Jebbink MF, Petersen G, Forster J, Berkhout B, Uberla K. Croup is associated with the novel coronavirus NL63. *PLoS Med* 2005;2:e240.
5. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012;367:1814–1820.
6. Oosterhof L, Christensen CB, Sengeløv H. Fatal lower respiratory tract disease with human corona virus NL63 in an adult haematopoietic cell transplant recipient. *Bone Marrow Transplant* 2010;45:1115–1116.
7. Arden KE, Nissen MD, Sloots TP, Mackay IM. New human coronavirus, HCoV-NL63, associated with severe lower respiratory tract disease in Australia. *J Med Virol* 2005;75:455–462.
8. Hamman L, Rich AR. Fulminating diffuse interstitial fibrosis of the lungs. *Trans Am Clin Climatol Assoc* 1935;51:154–163.
9. Bouros D, Nicholson AC, Polychronopoulos V, du Bois RM. Acute interstitial pneumonia. *Eur Respir J* 2000;15:412–418.
10. Galante O, Abramovich E, Nevo-Shor A, Almog Y. Hantavirus pulmonary syndrome in an Israeli man returning from South America. *Isr Med Assoc J* 2014;16:259–261.

FAIM3:PLAC8 Ratio Compared with Existing Biomarkers for Diagnosis of Severe Community-acquired Pneumonia: Comparing Apples to Oranges?

To the Editor:

We read with interest the article by Scicluna and colleagues (1) that describes a novel genomic marker to assist in rapid diagnosis of community-acquired pneumonia (CAP). The authors suggest that *FAIM3:PLAC8* ratio performed better