THE AMERICAN JOURNAL of MEDICINE®

Cold Agglutinin Syndrome Associated with a 2009 Influenza A H1N1 Infection

To the Editor:

In October 2009, a 60-year-old woman with end-stage diabetic nephropathy presented with malaise, dyspnea, and generalized edema. She was 10 kg over her usual weight and was unresponsive to high-dose furosemide.

On initial examination, she was apyretic, tachypneic with a digital pulse oximetry saturation of 95% on room air, tachycardic with positive abdominojugular test. She had bilateral symmetrical basal crepitations. The chest radiograph showed cardiomegaly, increased vascular markings, and interstitial infiltrates, suggesting hemodynamic pulmonary edema.

During the first dialysis session, she lost 2 kg but suddenly developed a fever of 40°C, with shivering and severe hypoxemia. Auscultation revealed predominantly right basal crepitations. A chest radiograph showed alveolar-interstitial infiltrates in the lower-right field. Empirical antibiotic therapy with ceftriaxone and spiramycin was started after bacteriological investigation.

Low hemoglobin levels (69 g/L [normal, 120-170]) with high reticulocyte counts (164 × 10^9/L) and low serum haptoglobin levels (0.21 g/L [normal, 0.34-2]) suggested acquired hemolytic anemia. Autoagglutination of anticoagulated blood samples resulted in a diagnosis of cold agglutinin hemolytic anemia; this diagnosis was supported by the direct antiglobulin test, which was positive using anti-C3 and negative using anti-immunoglobulin (IgG) antibodies, and the presence of cold agglutinins with anti-I specificity, 1/320 titers, and high thermal amplitude. Protein electrophoresis revealed no monoclo-

Funding: None.

Conflict of Interest: None of the authors have any conflicts of interest associated with the work presented in this manuscript.

Authorship: All authors had access to the data and played a role in writing this manuscript.

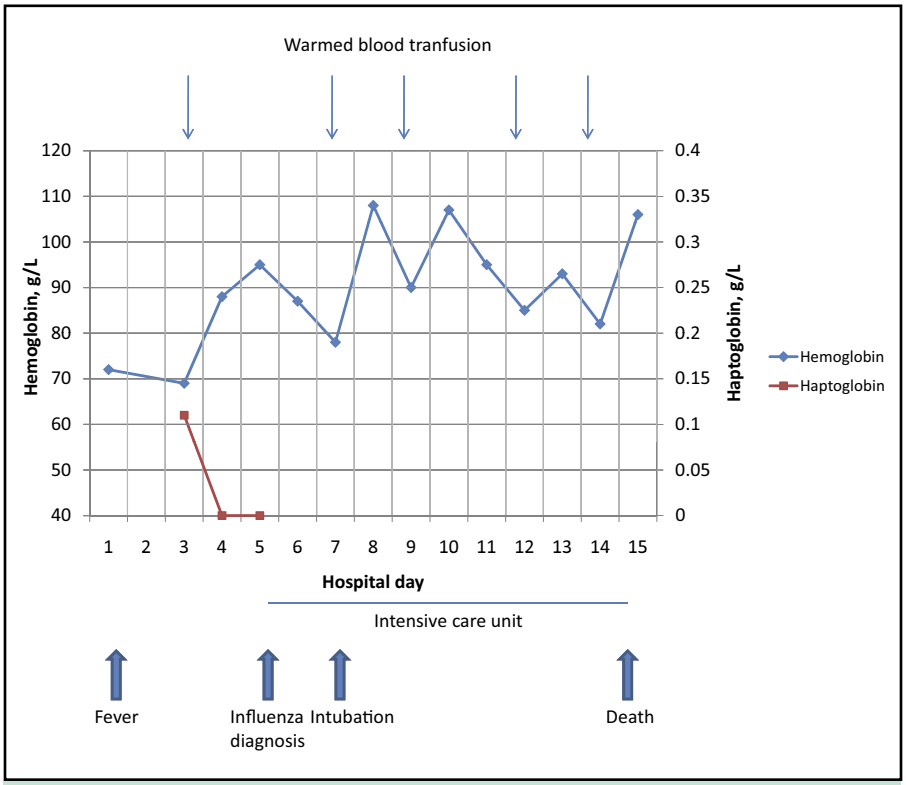

Figure Hemoglobin and haptoglobin levels during the hospital course.

nal gammapathy. Serodiagnosis for *Mycoplasma pneumoniae* was positive for specific IgG but negative for immunoglobulin M (IgM), excluding current infection. The legionella urinary antigen assay was negative. She received warmed blood (Figure) and was dialyzed against 37°C dialysate.

Despite antibiotic therapy and further intradialytic weight loss, she remained febrile and her respiratory status worsened. A new chest radiograph revealed bibasal alveolar infiltrates. Real-time reverse-transcriptase polymerase chain reaction on sputum was positive for the 2009 influenza A H1N1 virus. She received 30 mg oseltamivir after each hemodialysis session, but rapidly required mechanical ventilation for hypoxemic respiratory failure and died within a few days of contracting a secondary infection caused by *Acinetobacter baumannii*.

DISCUSSION

To our knowledge, this is the first report of cold agglutinin syndrome in a patient infected with the 2009 pandemic influenza A H1N1 virus.

Cold antibody autoimmune hemolytic anemias primarily include paroxysmal cold hemoglobinuria and cold agglutinin syndrome.[1] Paroxysmal cold hemoglobinuria is a rare condition and typically occurs in young children after a viral illness. The hemolytic antibody is a polyclonal IgG directed against the P-antigen on the red cell membrane; it activates the complement cascade, causing severe intravascular hemolysis.[2]

Cold-agglutinin syndrome is mediated, in 90% of patients, by an IgM molecule, which binds the red blood cell surface and activates the complement cascade, causing them to be coated with C3b. The C3b binds to C3b receptors in the mononuclear macrophage system causing extravascular hemolysis predominantly in the liver. Cold agglutinin disease is a monoclonal IgM-associated disorder, usually complicating low-grade lymphoproliferative disorders.[3] Polyclonal IgM antibodies usually occur after infections and are seen most notably with *Mycoplasma pneumoniae* and Epstein–Barr virus infections, but also with rubella, varicella, cytomegalovirus, human immunodeficiency virus infection, and Legionnaires' disease.[1]

Before the availability of serological techniques, detection of cold agglutinins was considered a valuable tool for *Mycoplasma pneumoniae* diagnosis.[4] However, our patient did not have such an infection. During a pandemic, physicians should be aware that cold agglutinin hemolysis might also be associated with 2009 influenza A H1N1 infection. The presence of cold agglutinin syndrome should not lead to the misdiagnosis of potentially fatal influenza-associated pneumonia, delaying the initiation of antiviral therapy.

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doi:10.1016/j.amjmed.2010.05.015

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