Case 11

This 35-year-old physician living in Boston was in his usual state of good health, having never missed a day of work, when he developed the abrupt onset of headache, fever, and body aches during the month of October. He subsequently noted a sore throat and a nonproductive cough. His travel history was unremarkable and he had no known tick exposure.

Physical examination was notable for a temperature of 38.9°C, but was otherwise unremarkable. The physician sent acute- and convalescent-phase serum specimens on himself to the state laboratory for antibody testing. Titers of his acute-phase serum to influenza A and B virus were both <8 by complement fixation. Convalescent-phase titers were 32 for influenza A and <8 for influenza B.

1. What is the etiology of infection in this patient?

2. Other than by serologic means, how can the laboratory diagnosis of this infection be established?

3. Other than as a self-limited upper respiratory tract infection, how can infections with this virus present?

4. What other types of this virus infect humans? Which of these are more common? Less common?

5. How does the virus infecting this patient change over time?

6. What groups of people are at high risk for developing serious, often life-threatening infections with this virus? What methods can be used to prevent this infection in these patients?

11 Case Discussion

1 and 2. This patient's clinical syndrome is consistent with an influenza viral infection. His fourfold rise in titer to influenza A virus indicates that he was infected with that virus. Interestingly, this physician was the sentinel case of influenza A for the state of Massachusetts in the year that he was ill. In most cases of uncomplicated influenza, the diagnosis of influenza is not established on the basis of laboratory testing, but is suspected on the basis of a compatible illness in a patient when influenza activity has been documented in the community. Obviously, for the sentinel, or first case of influenza A virus, as well as for patients in hospitals and institutions in which the possibility of epidemic spread exists, a more specific testing methodology is needed. This is also the case for patients in whom the diagnosis is uncertain and a definitive diagnosis would alter therapy.

Laboratory testing that can be used to establish the diagnosis of an influenza viral infection includes, most specifically, the isolation of the virus. In addition to serum for antibody studies, the physician sent his throat washings, from which influenza A virus was isolated. Isolation of influenza viruses can be performed in tissue culture. Because some influenza viruses will not cause a distinct cytopathic effect, hemagglutination or hemadsorption testing is used in those cultures in which a cytopathic effect is not present. Another methodology used to isolate influenza viruses is the inoculation of embryonated chicken eggs.

Because the isolation of influenza viruses takes a minimum of several days, more rapid methodologies are often preferred in the clinical laboratory. Detection of influenza antigens in epithelial cells obtained from a nasopharyngeal aspirate, wash, or swab can be performed using either an enzyme immunoassay (EIA) methodology or immunofluorescence (IF). Both of these methods are commercially available and have a rapid turnaround time. The advantage of the EIA is that a fluorescence microscope is not needed. The advantage of IF is that the quality of the specimen can be determined while viewing the specimen under the microscope. If there are an inadequate number of epithelial cells in the specimen, another specimen should be obtained.

Additional methods that are not routinely available include the use of reverse transcriptase PCR (polymerase chain reaction) and immune electron microscopy.

3. In addition to an uncomplicated infection, patients with influenza may have pulmonary complications. Primary influenza viral pneumonia, in which the disease progresses to involve both lungs, is associated with a high mortality. A secondary bacterial pneumonia can also occur in patients with influenza infection. The most common bacterial agents of this "superinfection" are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*. (Interestingly, this last bacterium got its name during the 1918 worldwide influenza pandemic. It was mistakenly thought to be the cause of the epidemic because it was recovered from the respiratory tract of infected patients. In some it probably represented nothing more than resident oropharyngeal flora, while in others, it may have been causing secondary

bacterial superinfections.) Croup is another syndrome that may occur due to influenza A infection.

Nonpulmonary complications of influenza infection are less common and include myocarditis (due to influenza A and B), Guillain-Barré syndrome following influenza A infection (and, rarely, following immunization against influenza), and Reye's syndrome in children. Reye's syndrome, in which hepatic and central nervous system abnormalities occur, has been associated with the use of salicylates in chidren with either influenza or varicella-zoster virus infection.

4. In addition to influenza A virus (the most common and most likely to be severe), infection can occur with influenza B virus (also common) and with influenza C virus (less common, less severe, and does not occur in epidemics).

5. Changes in the antigenic structure of influenza A occur over time. These can be divided into less dramatic changes, called antigenic drift, and major changes called antigenic shifts. Antigenic variation is due to changes in two proteins on the surface of the virus, the hemagglutinin (H) glycoprotein and the neuraminidase (N) glycoprotein. A total of three subtypes of hemagglutinin (H1, H2, and H3) and two subtypes of neuraminidase (N1 and N2) have been found in isolates known to cause human influenza A virus epidemics.

Small changes in the H and N antigens, due to the accumulation of point mutations resulting in amino acid substitutions, are responsible for antigenic drift. For influenza A virus, these changes will not necessarily result in the change of the classification of a viral strain (which is based upon the subtypes of the H and N antigens), but it may be sufficient to render patients with antibodies to the parent strain susceptible to the new mutant strain. This is the basis for the decision to reevaluate the formulation of the influenza vaccine on an annual basis and potentially to change it to include recent isolates, so that protective antibodies to the most recent isolates will be made in response to the vaccine.

The more dramatic antigenic shift is due to the genetic reassortment of genes encoding the H and N antigens. Since the influenza virus contains a segmented RNA genome, coinfection of a cell with two different influenza A viruses can result in many different possible reassortments via the exchange of RNA segments. This may result in a new virus that differs dramatically in one or both of these antigens from the parent strains. Historically, antigenic shift (for example, a change from H2N2 to H3N2 in 1968) has been responsible for worldwide epidemics (pandemics) due to the susceptibility of much of the world's population to the new virus. This reassortment may occur in animals, such as pigs and birds.

6. Groups that are at increased risk for having a poor outcome from an influenza infection include pregnant women, the elderly, residents of nursing homes and other chronic-care facilities, and people with chronic pulmonary or cardiovascular illnesses or any of a variety of metabolic diseases. Other groups that should be tar-

geted to receive the influenza vaccine include health care providers and close contacts of high-risk persons. Ideally, infection will be prevented by the current inactivated trivalent influenza vaccine. Unfortunately, not all patients in whom the vaccine is indicated receive it and, in those immunized, protection is not universal. One contraindication to the influenza vaccine is an allergy to eggs. In such patients, as well as those who are susceptible to influenza for other reasons, an additional possibility is the use of the antiviral agents amantadine or rimantadine for prophylaxis. These agents can also be used for treatment of influenza A infection if therapy is initiated early in the course of illness.

References

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