

## CLINICAL PRACTICE

## Infectious Mononucleosis

Katherine Luzuriaga, M.D., and John L. Sullivan, M.D.

*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

**A 16-year-old, previously healthy girl presents with a several-day history of fever, sore throat, and malaise. She appears very tired and has a temperature of 39°C. A physical examination is remarkable for diffuse pharyngeal erythema with moderately enlarged tonsils and the presence of several enlarged, tender anterior and posterior cervical lymph nodes. How should this case be managed?**

## THE CLINICAL PROBLEM

Infectious mononucleosis is a clinical syndrome that is most commonly associated with primary Epstein–Barr virus (EBV) infection. EBV is a gamma herpesvirus with a double-stranded DNA genome of about 172 kb.<sup>1</sup> Natural EBV infection occurs in humans only and results in a lifelong infection. Although the overwhelming majority of cases of infectious mononucleosis occur during primary EBV infection, infectious mononucleosis syndromes have also been reported in chronically infected persons after T-lymphocyte depletion with monoclonal antibodies against CD3.<sup>2</sup>

Seroepidemiologic surveys indicate that over 95% of adults worldwide are infected with EBV. In industrialized countries and higher socioeconomic groups, half the population has primary EBV infection between 1 and 5 years of age, with another large percentage becoming infected in the second decade. Primary EBV infections are rare in the first year of life, presumably because of high maternal seroprevalence and the protective effect of passively transferred maternal antibodies. In developing countries and lower socioeconomic groups, most EBV infections occur in early childhood. Primary infections in young children are often manifested as nonspecific illnesses; typical symptoms of infectious mononucleosis are uncommon.<sup>3</sup>

Infectious mononucleosis most commonly affects those who have primary EBV infection during or after the second decade of life. Because economic and sanitary conditions have improved over past decades, EBV infection in early childhood has become less common, and more children are susceptible as they reach adolescence. For example, rates of seroprevalence among children 5 to 9 years of age in urban Japan dropped from over 80% in 1990 to 59% from 1995 to 1999.<sup>4</sup> The overall incidence of infectious mononucleosis in the United States is about 500 cases per 100,000 persons per year, with the highest incidence in the age group of 15 to 24 years. A total of 30 to 75% of college freshmen are seronegative for EBV.<sup>5</sup> Each year, approximately 10 to 20% of susceptible persons become infected; infectious mononucleosis develops in 30 to 50% of these persons. There are no obvious annual cycles or seasonal changes in incidence, and there is no apparent predisposition on the basis of sex.

From the Department of Pediatrics and Program in Molecular Medicine (K.L., J.L.S.) and the Office of the Vice Provost for Research (J.L.S.), University of Massachusetts Medical School, Worcester. Address reprint requests to Dr. Luzuriaga at the University of Massachusetts Medical School, 373 Plantation St., Suite 318, Worcester, MA 01605, or at katherine.luzuriaga@umassmed.edu.

This article (10.1056/NEJMcp1001116) was updated on October 6, 2010, at NEJM.org.

N Engl J Med 2010;362:1993-2000.

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**PATHOGENESIS OF INFECTIOUS MONONUCLEOSIS**

EBV transmission occurs predominantly through exposure to infected saliva, often as a result of kissing and less commonly by means of sexual transmission.<sup>6</sup> The incubation period, from the time of initial exposure to the onset of symptoms, is estimated at 30 to 50 days. Lytic infection of tonsillar crypt epithelial cells, B lymphocytes, or both results in viral reproduction and high levels of salivary shedding,<sup>7,8</sup> which decrease over the first year of infection but persist for life.<sup>9</sup> Latently infected memory B lymphocytes circulate systemically and serve as lifelong viral reservoirs<sup>10,11</sup>; such lymphocytes transiently express only a highly restricted set of EBV genes,<sup>12</sup> and thus are largely inapparent to immune-surveillance cells. Vigorous responses to EBV by CD4+ and CD8+ T lymphocytes are expanded in patients with infectious mononucleosis.<sup>13-15</sup> Evidence suggests that these cellular immune responses limit primary EBV infection and control chronic infection but may also contribute to the symptoms of infectious mononucleosis.<sup>8,16</sup>

**NATURAL HISTORY AND COMPLICATIONS OF INFECTIOUS MONONUCLEOSIS**

The majority of patients with infectious mononucleosis recover without apparent sequelae. Published descriptions of the natural history of infectious mononucleosis vary, owing to differences in study populations, criteria for the diagnosis of infectious mononucleosis, and methods used. Prospective studies<sup>17-19</sup> indicate that most clinical and laboratory findings resolve by 1 month after diagnosis, but cervical adenopathy and fatigue may resolve more slowly. Though persistent fatigue (for 6 months or longer) with functional impairment has been described, most patients resume usual activities within 2 or 3 months.<sup>7,18</sup>

Infectious mononucleosis may be associated with several acute complications.<sup>20</sup> Hematologic complications, observed in 25 to 50% of cases of infectious mononucleosis, are generally mild and include hemolytic anemia, thrombocytopenia, aplastic anemia, thrombotic thrombocytopenic purpura or the hemolytic-uremic syndrome, and disseminated intravascular coagulation. Neurologic complications, which occur in 1 to 5% of cases, include the Guillain-Barré syndrome, facial-nerve palsy, meningoencephalitis, aseptic meningitis, transverse myelitis, peripheral neuritis, cerebellitis, and optic neuritis. Other rare but potentially life-threatening complications include

splenic rupture (in 0.5 to 1% of cases) and upper airway obstruction (in 1% of cases) due to lymphoid hyperplasia and mucosal edema.

Although primary EBV infection is rarely fatal, fulminant infection may occur. EBV is a common infectious trigger of hemophagocytic lymphohistiocytosis, which is clinically characterized by prolonged fever, lymphadenopathy, hepatosplenomegaly, rash, hepatic dysfunction, and cytopenia.<sup>21,22</sup> In a recent Japanese nationwide survey,<sup>23</sup> the incidence of hemophagocytic lymphohistiocytosis was estimated at 1 case in 800,000 persons; half of all cases were associated with EBV. EBV-associated hemophagocytic lymphohistiocytosis was observed in infants, children, and adults, but 80% of the cases occurred in children 1 to 14 years of age. Genetic defects in cellular cytotoxicity pathways and aberrant regulation of inflammatory responses have been identified in some infants and children with hemophagocytic lymphohistiocytosis.<sup>21</sup>

Male patients with the X-linked lymphoproliferative syndrome appear normal until primary EBV infection occurs, resulting in very severe or fatal infectious mononucleosis. Hypogammaglobulinemia, B-lymphocyte lymphoma, or both often develop in survivors. The gene responsible for the X-linked lymphoproliferative syndrome (*SH2D1A*, the SH2 domain-containing 1A gene) has been identified; it encodes a 128-amino-acid protein, which plays an important role in signal-transduction pathways in T lymphocytes.<sup>24</sup> A mutation in *SH2D1A* prevents normal activation-induced cell death, resulting in uncontrolled proliferation of CD8+ T lymphocytes.<sup>25</sup>

**STRATEGIES AND EVIDENCE****DIAGNOSIS**

Sore throat and malaise or fatigue are the most common presenting symptoms of infectious mononucleosis.<sup>18,26</sup> Pharyngitis (usually subacute in onset), fever, and lymphadenopathy constitute the classic triad of presenting signs.<sup>27</sup> Palatal petechiae, periorbital edema, and rash are less common. Splenomegaly is variably detected (in 15 to 65% of cases) on examination but is present in most cases on ultrasonography. Vaginal ulcers may be present in female patients.<sup>28</sup>

Pharyngitis accounts for up to 6% of all outpatient visits.<sup>29</sup> Features that may be useful in distinguishing pharyngitis due to infectious mononucleosis from pharyngitis from other causes are summarized in Table 1.

**Table 1. Differential Diagnosis of Pharyngitis.\***

Pathogen	Affected Age Group	Season†	Associated Diagnosis and Distinguishing Feature‡
<b>Respiratory viruses</b>			
Rhinovirus	All	Fall and spring	Common cold
Coronavirus	Children	Winter	Common cold
Influenza virus	All	Winter and spring	Influenza
Adenovirus	Children, adolescents, and young adults	Summer (outbreaks) and winter	Pharyngoconjunctival fever
Parainfluenza virus	Young children	Any	Fever, cold, croup
<b>Other viruses</b>			
Epstein-Barr virus	Adolescents and adults	Any	Infectious mononucleosis (80%)
Cytomegalovirus	Adolescents and adults	Any	Heterophile antibody–negative mononucleosis (5 to 7%) No or mild pharyngitis, anicteric hepatitis
Herpes simplex virus	Children	Any	Gingivostomatitis
Coxsackievirus A	Children	Summer	Herpangina, hand-foot-mouth disease
Human immunodeficiency virus	Adolescents and adults	Any	Heterophile antibody–negative (<1%) Mucocutaneous lesions, rash, diarrhea
Human herpesvirus 6	Adolescents and adults	Any	Heterophile antibody–negative (<10%)
<b>Bacteria</b>			
Group A streptococci	School-age children, adolescents, and young adults	Winter and early spring	Scarlatiniform rash, no hepatosplenomegaly
Group C and group G streptococci	School-age children, adolescents, and young adults	Winter and early spring	Scarlatiniform rash
<i>Arcanobacterium haemolyticum</i>	Adolescents and young adults	Fall and winter	Scarlatiniform rash
<i>Corynebacterium diphtheriae</i>		Fall and winter	Tonsillar, pseudomembrane myocarditis
<i>Neisseria gonorrhoeae</i>	Adolescents and adults	Any	Tonsillitis
<i>Mycoplasma pneumoniae</i>	School-age children, adolescents, and young adults	Any	Pneumonia, bronchitis
<b>Parasites</b>			
<i>Toxoplasma gondii</i>	Adolescents and adults	Any	Heterophile antibody–negative (<3%) Small, nontender anterior lymphadenopathy

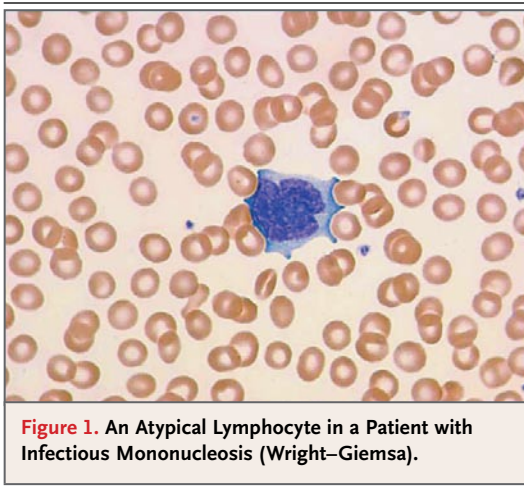
\* Data are from Alcaide and Bisno.<sup>29</sup>

† Season is applicable only in temperate climates.

‡ Numbers in parentheses indicate the approximate percentage of mononucleosis cases due to the given pathogen.

Infection with group A streptococci is the most common bacterial cause of pharyngitis, accounting for 15 to 30% of pharyngitis cases in children and 10% of cases in adults; its highest incidence is among children 5 to 15 years of age. Distinguishing infection with group A streptococci from infectious mononucleosis is important, since antimicrobial therapy is warranted in cases of pharyngitis from group A streptococcal infection to prevent acute rheumatic fever, reduce suppurative complications, and reduce infectivity; therapy may also modestly alleviate clinical symptoms and shorten the clinical course.<sup>30,31</sup> Thus, it is reason-

able to screen patients who have suspected infectious mononucleosis for group A streptococcal infection with the use of a throat swab and rapid antigen testing or culture. Although cases of concomitant group A streptococcal infection and infectious mononucleosis have been reported, their true frequency is uncertain, since a positive rapid test or culture in a patient with infectious mononucleosis may indicate colonization. Morbilliform rashes are common in patients with infectious mononucleosis treated with amoxicillin or ampicillin (occurring in up to 95% of patients with such drug exposure) and other  $\beta$ -lactam antibi-



**Figure 1.** An Atypical Lymphocyte in a Patient with Infectious Mononucleosis (Wright–Giemsa).

otics (40 to 60%); this should be taken into account when considering which antibiotic to administer in patients with possible infectious mononucleosis.

The differential diagnosis of mononucleosis syndromes (which are characterized by pharyngitis, lymphadenopathy, and malaise) is more limited and includes primary infection with the human immunodeficiency virus (HIV), human herpesvirus 6 (HHV-6), cytomegalovirus, or *Toxoplasma gondii*. Common laboratory findings in patients with infectious mononucleosis include marked lymphocytosis (>50% leukocytes) with atypical lymphocytes (Fig. 1). The detection of at least 10% atypical lymphocytes on a peripheral-blood smear in a patient with mononucleosis has a sensitivity of 75% and a specificity of 92% for the diagnosis of infectious mononucleosis.<sup>26</sup> Aminotransferase levels may be elevated in older children and adults; hyperbilirubinemia and jaundice are uncommon.

Primary EBV infection induces the activity of a heterogeneous group of circulating heterophile (IgM) antibodies directed against viral antigens that cross-react with antigens found on sheep and horse red cells. Rapid (monospot) tests for these heterophile antibodies are used to screen patients for infectious mononucleosis.<sup>32</sup> Heterophile antibody tests are negative in 25% of patients during the first week of infection and in 5 to 10% during or after the second week; once antibodies are present, they may persist for a year or more. Heterophile antibody tests are positive in only 25 to 50% of children under 12 years of age. In the presence of mononucleosis symptoms, a positive heterophile antibody test has a sensitivity of approximately 85% and a specificity of approxi-

mately 94% for the diagnosis of infectious mononucleosis. Heterophile antibody tests are usually negative in patients who have mononucleosis syndromes associated with primary infection with cytomegalovirus (CMV), HHV-6, or toxoplasma; heterophile antibodies have been reported only rarely in patients with primary HIV type 1 infection (in <1%).<sup>33,34</sup>

Thus, a diagnosis of infectious mononucleosis can be confirmed in most adolescents on the basis of the clinical presentation, the presence of atypical lymphocytes on a peripheral-blood smear, and a positive heterophile antibody test. However, patients with risk factors for acute HIV infection should be screened with the use of tests that detect HIV nucleic acids.<sup>35</sup> Given the adverse fetal outcomes associated with primary CMV and toxoplasma infections during pregnancy and the risk of mother-to-child transmission of HIV, definitive testing (antibody testing for EBV infection, IgM antibody and nucleic acid testing for CMV infection, and nucleic acid–based testing for HIV) is indicated in pregnant women presenting with mononucleosis.

A definitive diagnosis of EBV infection can be made by testing for specific IgM and IgG antibodies against viral capsid antigens, early antigens, and EBV nuclear antigen proteins (Fig. 2).<sup>36</sup> Responses of IgM against viral capsid antigens are commonly detected on presentation with symptoms, and evidence of such responses disappears within 4 to 8 weeks; IgM antibodies are not detected in association with chronic infection, so their presence is virtually diagnostic of primary EBV infection. Titers of IgG antibody against viral capsid antigens are detectable at the time of, or shortly after, presentation with infectious mononucleosis and persist at reduced levels throughout life. IgG directed against early lytic-cycle proteins (e.g., early antigen D) tends to appear in association with the peak IgM response, reaching maximal levels after the IgM response; antibodies against early antigens usually disappear by 3 to 6 months after the onset of infectious mononucleosis but persist in 20% of healthy persons for years. IgG antibodies against EBV nuclear antigen usually are not detectable until several weeks after the onset of infectious mononucleosis.

#### MANAGEMENT

On the basis of clinical experience, supportive care is recommended for patients with infectious mononucleosis. Acetaminophen or nonsteroidal

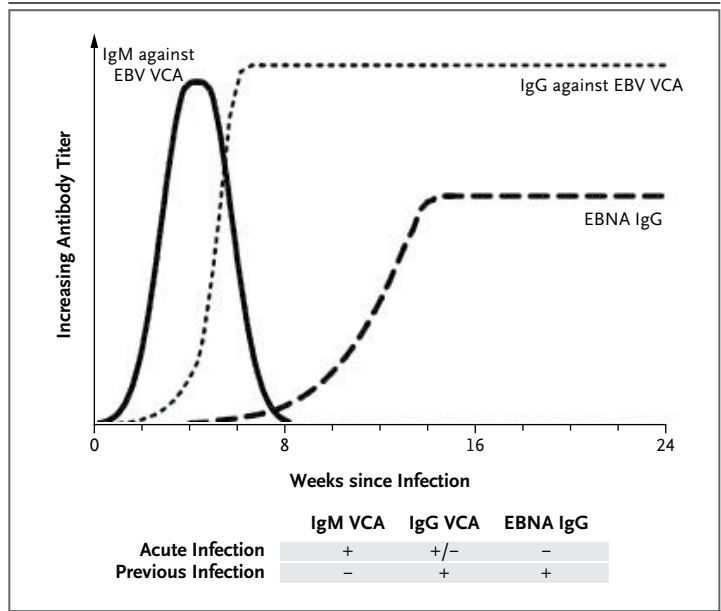
antiinflammatory agents are recommended to manage fever, throat discomfort, and malaise. Adequate fluid intake and nutrition should also be encouraged. Although getting adequate rest is prudent, bed rest is unnecessary. Patients may excrete high levels of EBV in their saliva in the year after the onset of infectious mononucleosis, but special precautions against transmission of EBV are not necessary, since most people are EBV-seropositive.

The majority of reported splenic ruptures, a widely feared complication of infectious mononucleosis, have occurred within 3 weeks after diagnosis, but rupture has been reported to occur as late as 7 weeks after diagnosis.<sup>37</sup> Most athletes do not feel well enough to participate in sports until the 3rd or 4th week of illness; avoidance of exertion, including participation in sports, for at least 3 weeks is generally recommended.<sup>37</sup> There is uncertainty regarding the appropriate time to resume participation in contact sports. Physical examination to detect splenomegaly is often unreliable; though ultrasonography can be used, a direct relationship between splenic size in patients with infectious mononucleosis and the risk of splenic rupture has not been established. Given the rarity of splenic rupture after 3 weeks, a recent review has suggested that patients may consider a return to contact sports a minimum of 3 weeks after the onset of symptoms or once they are afebrile, after clinical symptoms and findings have resolved, or when they feel well enough to play.<sup>37</sup>

AREAS OF UNCERTAINTY

**ANTIVIRAL TREATMENT OF INFECTIOUS MONONUCLEOSIS**

There is great interest in developing antiviral regimens for treating infectious mononucleosis. At least five randomized, controlled trials of acyclovir treatment for infectious mononucleosis have shown a transient reduction in oropharyngeal viral shedding during treatment, with a rebound after discontinuation of treatment; acyclovir use did not significantly reduce peripheral-blood EBV levels or the duration or severity of clinical symptoms.<sup>38</sup> A recent, randomized, pilot study comparing valacyclovir with no treatment in 20 young adults with infectious mononucleosis showed a transient decrease of oropharyngeal EBV shedding during therapy and a reduction in the number and severity of reported symptoms in the valacy-



**Figure 2. Levels of Antibodies Specific to Epstein-Barr Virus (EBV) during Infectious Mononucleosis and Convalescence.**

EBNA denotes EBV nuclear antigen, and VCA viral capsid antigens.

clovir group, but with no difference between the two groups in the peripheral-blood EBV load.<sup>39</sup> Larger randomized, blinded, placebo-controlled trials are necessary to verify these results.

A recent report described reduced frequencies of EBV-infected memory B lymphocytes in the peripheral blood of persons with chronic EBV infection who received valacyclovir therapy for 1 year, as compared with untreated controls.<sup>40</sup> EBV episomal replication occurs through homeostatic proliferation of memory B lymphocytes; this episomal replication is mediated by the host's DNA polymerase and is thus not susceptible to antiviral inhibition. Lytic viral replication in the oropharynx or after the reactivation of memory B lymphocytes is mediated by viral DNA polymerase, which is susceptible to antiviral inhibition. This suggests that maintenance of the memory B lymphocyte EBV reservoir depends at least partly on new episodes of EBV lytic replication. On the basis of the 1-year data, the authors estimated that it would take at least 11 years of daily valacyclovir therapy to clear an EBV infection.

**CORTICOSTEROIDS FOR TREATING INFECTIOUS MONONUCLEOSIS**

Some experienced clinicians have advocated the use of corticosteroids for treatment of uncomplicated infectious mononucleosis, but the data sup-

porting this approach are limited. A Cochrane review<sup>41</sup> evaluated seven randomized, clinical trials that compared the effectiveness of corticosteroids with that of placebo (four trials) or other interventions (three trials) for control of symptoms. Most of the studies were small (24 to 94 subjects), and the substantial variability among the diagnostic criteria, corticosteroid regimens, analytic methods, and outcome measures precluded direct comparisons. Two studies<sup>42,43</sup> showed significant early improvement (12 hours after administration) of sore throat among corticosteroid recipients as compared with placebo recipients; however, the effects were not sustained at a follow-up visit. One trial<sup>44</sup> showed a shorter duration of fever in corticosteroid-treated patients than in placebo recipients. Overall, the authors concluded that there was insufficient evidence of a clinically relevant benefit to recommend corticosteroid treatment; they also noted a lack of information regarding the potential adverse effects of treatment.<sup>41</sup>

Clinical experience suggests that corticosteroids may be helpful in the management of more severe complications of infectious mononucleosis, including upper-airway obstruction, hemolytic anemia, and thrombocytopenia, although randomized, clinical trials evaluating their efficacy are limited.

#### VACCINES AGAINST EBV INFECTION

Efforts are being made to develop an EBV vaccine. In a recent phase 2, randomized, placebo-controlled trial of a glycoprotein-350–subunit vaccine, vaccine recipients were not protected against acquiring infection, but were less likely to have symptoms of infectious mononucleosis during primary EBV infection, as compared with patients who were not vaccinated.<sup>45</sup>

#### TREATMENT OF LYMPHOPROLIFERATIVE DISORDERS ASSOCIATED WITH PRIMARY EBV INFECTION

A detailed discussion of the management of the rare disorders hemophagocytic lymphohistiocytosis and the X-linked lymphoproliferative syndrome is beyond the scope of this article. Briefly, in a retrospective study of 20 cases of EBV-associated hemophagocytic lymphohistiocytosis, treatment with etoposide was associated with reduced mortality.<sup>46</sup> Prospective trials are currently evaluating treatment strategies for acute hemophagocytic lymphohistiocytosis (ClinicalTrials.gov numbers, NCT00426101 and NCT00334672); these trials involve chemotherapy (i.e., etoposide, cy-

closporine, and corticosteroids), with stem-cell transplantation for cases that are refractory to medical treatment.<sup>47</sup> The X-linked lymphoproliferative syndrome can be diagnosed prenatally, and early bone marrow transplantation is recommended to correct this disorder.

#### EBV INFECTION AND AUTOIMMUNE DISORDERS OR CANCER

Associations have long been recognized between EBV infection and Burkitt's lymphoma or nasopharyngeal carcinoma. A history of symptomatic infectious mononucleosis has also been associated with an increase in the risk of multiple sclerosis by a factor of two<sup>48</sup> and of EBV-positive Hodgkin's lymphoma by a factor of four.<sup>49,50</sup> Further work is necessary to elucidate the role of EBV in these disorders.

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#### GUIDELINES

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To our knowledge, there are no professional-society guidelines for the evaluation and management of infectious mononucleosis.

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#### CONCLUSIONS AND RECOMMENDATIONS

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Infectious mononucleosis should be suspected in adolescents and young adults (10 to 30 years of age), such as the patient described in the vignette, who present with sore throat and malaise. Common signs include fever, lymphadenopathy, and pharyngitis. Laboratory studies that support a diagnosis of EBV-associated infectious mononucleosis include absolute and atypical lymphocytosis and a positive heterophile antibody test. In cases in which the diagnosis is unclear, EBV-specific serologic testing may be used to definitively diagnose primary EBV infection. Treatment is largely supportive; antiviral therapy is not recommended, and corticosteroids are not indicated for uncomplicated cases. The majority of patients with infectious mononucleosis recover without sequelae and return to normal activities within 2 months after the onset of symptoms. Since the majority of the population is EBV-positive, special precautions against transmission are not necessary.

Dr. Luzuriaga reports receiving consulting fees and grant support from Tibotec. No other potential conflicts of interest relevant to this article are reported.

We thank Adair Seager, M.D., and Hongbo Yu, M.D., Ph.D., of the Department of Pathology, University of Massachusetts Medical School, Worcester, for the photomicrograph in Figure 1.

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