Life-Threatening Leukocytoclastic Vasculitis with Pulmonary Involvement Due to Echovirus 7

We describe a previously healthy woman who developed life-threatening vasculitis manifested as pulmonary infiltrates and “palpable purpura” following a benign episode of upper respiratory tract infection. The healing herpangina lesions and signs of cutaneous vasculitis clued us in to the type of virus and the mechanism of immune-mediated damage, respectively. Therapy with high doses of steroids along with broad-spectrum antibiotics resulted in a good clinical outcome. The possible pathogenic mechanisms of virus-induced damage are discussed.

A 37-year-old woman with recent voluntary weight loss of 60 lb over a 6-month period during a liquid-protein diet developed sore throat, coryza, and fatigue ~9 days before admission. Five days earlier, she was at a Lake Arrowhead resort but had no insect bites or water contact. The upper respiratory tract symptoms resolved in 4 days. She was well until the day of admission when she developed a sudden onset of rhinorrhea, sore throat, dyspnea, pleuritic chest pain, hemoptysis, arthralgia, and skin lesions over both lower extremities.

Eight hours later she was admitted to the hospital. A chest roentgenogram showed bilateral pulmonary infiltrates; the partial pressure of oxygen while the patient was breathing room air was 68 mm Hg. A complete blood cell count was unremarkable except for a hemoglobin level of 11.5 g/dL and 5% band forms. The leucine aminopeptidase level was mildly elevated, but the rest of the serum chemistry analysis results, urinalysis results, erythrocyte sedimentation rate, and prothrombin and partial thromboplastin times were normal. Therapy with intravenous ceftriaxone and oral clarithromycin was started after blood and sputum specimens for cultures were obtained.

Twelve hours later, oxygenation deteriorated further requiring 100% O₂. A follow-up roentgenogram showed a marked increase in bilateral infiltrates involving 80% of the lung fields. Several healing vesicles were present on the hard palate. Approximately 20 palpable papules with petechial centers (ranging from 0.3 to 1 cm in size) were noted on the legs.

A clinical diagnosis of resolving herpangina and immune-mediated vasculitis was made. Therapy with intravenous methylprednisolone (100 mg) was administered every 6 hours. Biopsy of a skin lesion demonstrated florid leukocytoclastic vasculitis with extensive fibrinoid necrosis of the vessel wall. Blood and sputum cultures were negative. She felt better over the next 24 hours, and her O₂ requirement declined quickly. Methylprednisolone therapy was tapered on hospital day 4, when a chest roentgenogram showed marked improvement. She was discharged on hospital day 11 to finish a 2-week course of tapering prednisone therapy.

Additional studies of the sputum sample obtained during admission included negative direct fluorescent antibody staining for influenza virus types A and B, Legionella, Chlamydia pneumoniae, and respiratory syncytial virus. Testing for antinuclear antibody, antineutrophil cytoplasmic antibody, and anti–glomerular basement membrane antibody was negative. Viral cultures of throat washings and stool were negative. Testing for acute-phase and convalescent-phase antibodies to Mycoplasma pneumoniae, adenovirus, hantavirus, Coxsackie A virus, Coxsackie B viruses 1–6, and echoviruses 6, 9, 11, and 30 was negative. The titer of neutralizing antibody to echovirus 7 increased from 1:20 to 1:320; specimens for these determinations were obtained 10 days apart (titers were measured by associates of the Regional University Pathologist Laboratory, Salt Lake City, Utah). She continued to feel well 6 months after the infection, and the titer of antibody to echovirus 7 decreased to 1:80.

Leukocytoclastic vasculitis following infection has been well documented [1], but to our knowledge, there has not been a previous case attributed to echovirus 7. The biphasic illness seen in this patient is typical of enterovirus infection. The initial upper respiratory tract infection represents the minor enterovirus infection during which low-grade viremia frequently occurs as the virus replicates in the submucosal lymphatic tissue and lymphohematogenously disseminates to secondary sites [2]. In most cases, the infection clears after the minor illness (coinciding with the appearance of type-specific antibody), and recovery from herpangina is usually complete within 1 week of onset [3]. In few patients, however, the second phase begins with virus replication in the secondary sites, resulting in major viremia and a severe immune response that follows [2].

In our patient, extensive weight loss before the infection could have had a significant impact on the proper function of her immune system. A decrease in lymph node weight has been observed in malnourished animals, and the titer of neutralizing antibody to enterovirus in malnourished animals was low 7 days after Coxsackie B virus infection compared with those in normal controls, although this titer increased to a normal value 1 week later [4]. Type-specific neutralizing antibody to echovirus 7 was present in our patient at only a low titer at the onset of life-threatening vasculitis.

The putative receptor for echovirus 7 has been elucidated in recent years. Decay-accelerating factor or CD55 is a ubiquitous membrane-bound protein present on, but not limited to, vascular endothelial cells that participates in modulation of the activation of complement components C3 and C5 [5, 6]. One could speculate that free virus or virus-antibody complex binds to decay-accelerating factor on vascular endothelial cells during major viremia, strategically reducing the availability of this membrane-bound protein. The subsequent activation of the complement cascade by type-specific antibody bound to endothelial cells becomes unregulated, and the overwhelming complement-mediated damage leads to the manifestation of severe leukocytoclastic vasculitis.

Use of high doses of corticosteroids in this patient resulted in prompt improvement of her condition without exacerbating the viral infection. Intravenous immunoglobulin might have therapeutic efficacy in view of its anticomplement effect [7] but could have interfered with the serological diagnosis. Prompt recognition of life-threatening immune-mediated injury in the face of resolving enterovirus infection cannot be overemphasized. Institution of aggressive steroid therapy should be considered without delay when...
appropriate antibiotic therapy for possible bacterial superinfection has been started.

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References

Disseminated Toxoplasmosis After Liver Transplantation: Case Report and Review

Toxoplasma gondii is an important pathogen among organ transplant recipients. We describe a patient who died of disseminated toxoplasmosis following liver transplantation and review reports of similar cases in the literature.

A 53-year-old previously healthy woman underwent liver transplantation because of rapidly advancing fulminant hepatitis and hepatic coma. During the first 20 postoperative days, graft rejection and cytomegalovirus (CMV) antigenemia were diagnosed and treated. She was discharged from the hospital on the 26th posttransplant day with methylprednisolone, azathioprine, and cyclosporin A therapy. One month later she returned to the transplantation clinic because of deteriorating liver function. Therapy for acute rejection was unsuccessful. A stricture in the bile-duct anastomosis was detected and dilated endoscopically. The patient was discharged from the hospital and returned 5 days later with a fever due to sepsis and worsening liver function. There was no response to antimicrobial therapy and explorative laparotomy was performed because of suspected peritonitis. There were no signs of an acute abdomen. A repeated liver assay showed evidence of invasive candidiasis and returned 5 days later with a fever due to sepsis and worsening liver function. There was no response to antimicrobial therapy and transplant rejection was confirmed by advanced necrosis. Swollen ghost-like hepatocytes contained cysts filled with granular-appearing organisms that immunoperoxidase staining with a polyclonal Toxoplasma-specific antibody confirmed to be Toxoplasma species. Similar cysts were found in the myocardium and in the lungs. There was no evidence of toxoplasmosis or Pneumocystis carinii infection in the brain.

Direct microscopic evaluation of BAL fluid from the patient we described raised the suspicion of toxoplasmosis. Serologic evaluation and PCR assays of both pre- and postmortem specimens confirmed the diagnosis. Our patient had been toxoplasma-seropositive with high avidity indicating past immunity before the first liver transplantation. Serological follow-up showed a diagnostic rise in IgG antibodies to Toxoplasma, no IgM antibodies to Toxoplasma, and a consistently high IgG avidity, indicating a reaction before the second transplantation. The IgG avidity assay has shown its value in distinguishing primary from secondary infections and in timing the initial antigenic challenge [1]. To our knowledge, the patient we described is the first liver transplant recipient with reactivated toxoplasmosis verified by IgG avidity. Both donors were toxoplasma seronegative. PCR assays [2] showed Toxoplasma DNA in whole blood and in a liver biopsy obtained from the recipient before death.

The clinical manifestations appeared within 3 months of the transplantation in all reported cases of liver transplant recipients with disseminated toxoplasmosis (table 1). The first manifestation was fever, and pneumonia and multiorgan failure were observed most frequently. Among these six liver transplant patients the mortality rate was 83% (5 of 6 patients). In three cases, toxoplasmosis was diagnosed only at autopsy.

Antirejection treatments, CMV infection, and ganciclovir therapy may have contributed to the development of severe immunosuppression and predisposed the patient to T. gondii infection. In seropositive recipients, toxoplasmosis should be considered in the differential diagnosis of multiorgan failure during the early post–liver transplantation period because early initiation of therapy might be life-saving. We recommend that liver transplant candidates be screened for toxoplasma-specific antibodies. Because the lungs are among the three sites most commonly involved in disseminated toxoplasmosis [4], evaluation of BAL fluid should be undertaken for all immunosuppressed patients for whom there is a clinical suspicion of

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