Still's Disease, Severe Thrombocytopenia, and Acute Hepatitis Associated with Acute Parvovirus B19 Infection

The pathogenetic role of human parvovirus B19 infection in clinical conditions other than erythema infectiosum or aplastic crisis is often underestimated. We describe a patient with an unusual combination of clinical manifestations associated with primary acute B19 infection.

A 19-year-old man with an unremarkable medical history presented in September 1995 with a spiking fever and sore throat. A few days later, rash, conjunctivitis, and balanitis appeared, followed by myalgia, bilateral gonarthritis, and mild splenomegaly. A complete blood count showed neutrophilic leukocytosis (WBCs, 15 × 10^9/L); the hemoglobin level and platelet count were within the normal range. The patient's serum concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were also elevated. Serologies for common viral infections were negative. Rheumatoid factor, antinuclear antibodies, anti-DNA antibodies, and antibodies to streptolysin O were not detectable. The ferritin level was increased (1,694 ng/mL). An examination of bone marrow showed only moderate granulopoietic hyperplasia. A diagnosis of Still's disease was made at another hospital. Treatment with aspirin (2 g/d) and prednisone (60 mg/d) plus antibiotics for 20 days was totally ineffective. No change in the patient's clinical condition was observed except for the disappearance of the rash after 3 days.

Owing to a sudden decrease in the platelet count (80 × 10^9/L) and the persistence of the other clinical findings, the patient was admitted to our hospital on 2 October 1995. A complete blood count revealed the following values: hemoglobin, 96 g/L; WBCs, 4.9 × 10^9/L; and platelets, 1.0 × 10^9/L. Signs of disseminated intravascular coagulation or hemolysis were not detected. A bone marrow examination showed a mild reduction in erythroleukopoiesis, while megakaryopoiesis appeared markedly reduced. The bone marrow cell karyotype was normal. Platelet-associated immunoglobulins were not detected, and an antiglobulin test was negative. Levels of liver enzymes (AST, 200 IU/L; ALT, 460 IU/L) as well as serum ferritin (19,000 ng/mL) were elevated. Serologies were negative for common herpesviruses, including Epstein-Barr virus, cytomegalovirus, and human herpes virus 6; HIV 1 and HIV 2; and hepatitis A, B, C, and G viruses. The negative serologies were also confirmed by use of PCR.

ELISA for antibodies to B19 showed positivity for B19 IgG and negativity for B19 IgM. B19 DNA sequences were detected in the patient's serum with use of PCR, and B19 DNA was also identified in bone marrow cells by in situ hybridization.

A 4-day course of treatment with intravenous immunoglobulin (IVIG) was started (total dose, 100 g), together with packed platelets for the first 5 days. During the next 14 days, the serum concentrations of AST and ALT progressively decreased, and the clinical signs of Still's disease completely disappeared. However, the levels of platelets (20 × 10^9/L) and hemoglobin (66 g/L) and the WBC count (1.6 × 10^9/L) remained low. After a further treatment with IVIG (total dose, 100 g), the blood cell counts rapidly increased, reaching the normal range in the next 2 weeks (figure 1). After recovery, B19 DNA sequences were no longer detectable in either the patient’s serum or bone marrow, examination of which showed normal hematopoiesis. The patient is now in good health.

B19 is known to have tropism for erythroid precursors in bone marrow [1] and to cause either transient aplastic crises in immunocompromised hosts or mild thrombocytopenia in sporadic cases [2]. Furthermore, B19 has been recognized as a cause of acute hepatitis in children [3, 4]. Two possible pathogenetic mechanisms have been suggested: a direct toxic effect on the liver and/or bone marrow...
Transmission of Multidrug-Resistant Mycobacterium bovis to an Immunocompetent Patient

Human tuberculous infections caused by Mycobacterium bovis are relatively rare. Most cases among HIV-infected patients have been reported in England, France, and the United States [1], with human-to-human transmission [2]. Infections due to multidrug-resistant M. bovis are extremely rare, but recently two nosocomial outbreaks involving HIV-infected patients have been described at two different hospitals in Spain [3, 4]; in one hospital, there was transmission to a foreign, HIV-positive patient who stayed in Spain briefly [5]. However, such transmission to immunocompetent patients is extremely rare. We describe herein transmission of multidrug-resistant M. bovis to an immunocompetent patient.

A 46-year-old, heterosexual, HIV-negative, Spanish man was referred to our hospital in March 1996. He had a 2-month history of pleuritic chest pain and fever (temperature, 38°C–39°C) accompanied by a 7-kg weight loss. He denied exposure to mycobacterial disease. A chest radiograph showed a shadow in the right upper lobe with air bronchogram and a few cavitations inside. A CT scan of the thorax disclosed a shadow in the right lower lobe, a right pleural effusion, and pretracheal lymphadenopathy. A diagnosis of pulmonary tuberculosis was made on the basis of a positive auramine-fluorochrome stained smear of a bronchial brushing specimen. Treatment with isoniazid (300 mg/d), rifampin (600 mg/d), ethambutol (1,200 mg/d), and pyrazinamide (1,500 mg/d) was initiated. The latter two agents were discontinued after 2 months, and treatment with isoniazid and rifampin was maintained for 4 additional months, after which time he was asymptomatic. Because no sputum was produced during the treatment, no microbiological controls were done.

After 5 weeks of therapy, a culture positive for Mycobacterium tuberculosis complex (3 cfu) was obtained in Löwenstein-Jensen medium without sodium pyruvate and with 2-thiophenecarboxylic acid hydrazide, although these two media are usually inhibitory for M. bovis but not for M. tuberculosis. The strain was identified by using DNA-RNA hybridization (AccuProbe; Gen-Probe, San Diego, CA). At the end of treatment (September 1996), a chest radiograph showed progression of abnormalities and several small nodules in the left upper lobe. In November 1996, repeated bronchoscopy was performed. At this time, pulmonary biopsy, bronchial washing, and bronchial brushing samples were obtained; staining of these specimens was negative. In December 1996, the patient became symptomatic; a few sputa produced at that time stained positive for mycobacteria. A new treatment regimen with isoniazid (300 mg/d), streptomycin (750 mg/d), ethambutol (1,200 mg/d), rifampin (600 mg/d), ofloxacin (400 mg b.i.d.), and pyrazinamide (1,500 mg/d) was instituted; the latter was discontinued after 10 weeks.

Treatment was maintained until susceptibility test results were available, including those for the baseline strain and the last-cultured strain. Cultures of all the bronchoscopy samples and sputa yielded M. tuberculosis complex in 4 weeks, and all strains were resistant to isoniazid, rifampin, streptomycin, ethambutol, and pyrazinamide. Because multidrug-resistant M. bovis was suspected, the strain was sent to two reference centers for molecular typing and in vitro susceptibility tests for second-choice drugs. The M. bovis strain was also resistant “in vitro” to kanamycin, ethionamide, rifabutin, ofloxacin, amikacin, and clarithromycin.

The multidrug-resistant strain was typed by use of spoligotyping and restriction fragment length polymorphism (RFLP) analysis.