It was first noted in 1961 that lactic acidosis could occur in patients in whom neither shock nor hypoxemia was evident.[3] Lactic acidosis that occurs without clinical evidence of tissue hypoperfusion is classified as type B.[2] In 1963 type B lactic acidosis was described in patients with acute leukemia.[4] Since then, various hematologic malignant neoplasms have been reported to cause lactic acidosis. In addition, lactic acidosis has also been noted to occur with solid tumors (breast, colon, lung), usually in the presence of liver or bone marrow metastases.[5] Type B lactic acidosis has not, to our knowledge, been previously described in patients with multiple myeloma.

Although the ultimate cause of lactic acidosis is an imbalance between lactate production and use, the mechanism in malignant disorders is controversial. Lactate production is largely determined by glycolytic activity.[6] It has been postulated that in patients with cancer, glycolytic flux is stimulated by ischemia due to a tightly packed neoplastic tissue bed or leukemic microemboli.[7] It is also possible that increased lactate production is caused by a primary increase in glycolytic activity in neoplastic tissue. The association between malignant disease and abnormalities of glucose metabolism was initially described in 1925.[8] In 1930 it was noted that malignant cells showed accelerated glycolytic activity with the production of lactic acid.[9] It was proposed that cancer cells had decreased respiration that caused the cells to increase their glycolytic rate to maintain adenosine triphosphate production. Later studies supported the observations of increased glycolytic activity but found that tissue oxygenation and respiratory activity in neoplastic cells were intact.[10] This primary increase in glycolytic activity has been called aerobic glycolysis.[10] The reason why malignant cells choose to satisfy their energy demands in this way is not clear. Glycolytic activity in cancer cells is much less responsive to feedback regulation and proceeds at a higher rate than required by the Krebs cycle.[6,9] This may confer advantage to malignant cells by promoting unrestrained growth.[10]

A human myeloma cell line was used to show that glycolytic flux and lactate production were increased by insulin and insulinlike growth factor-1 (IGF-1).[11] The ability of insulin and IGF-1 to stimulate glycolysis and lactate production in myeloma cells may relate to the fact that plasma cells are derived from the same germ layer as tissues traditionally considered to be insulin sensitive—liver, muscle, and fat.[11] It is not clear, however, why lactic acidosis has not been previously noted in patients with multiple myeloma. Possibly only rare myeloma cell lines are capable of increasing lactate production enough to overwhelm utilization pathways.

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Hemorrhagic Fever With Renal Syndrome in California

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HANTAVIRUS DISEASE (HVD) encompasses the spectrum of illness caused by infection with viruses of the *Hantavirus* genus of Bunyaviridae.[1] Antibodies to hantaviruses have been demonstrated in human serum specimens throughout the world.[2] Until recently, hantavirus infection was thought either to be asymptomatic or to result in hemorrhagic fever with renal syndrome, an illness of varying severity characterized by fever, hypotension, acute renal failure, and thrombocytopenia.[3] The recent detection in the southwestern region of the United States of rising antibody titers to hantavirus in serum specimens from persons with unexplained acute respiratory failure shows that the clinical expression of hantavirus infection is broader than originally recognized.[4] Annually there are about 200,000 documented cases of hemorrhagic fever with renal syndrome worldwide, with nearly 50% of the cases in the People's Republic of China. Fewer cases occur in Korea, Russia, Scandinavia, Europe, and the Balkan region.[2] We describe a case of this illness confirmed in a California resident with a recent history of travel to Korea.

Report of a Case

The patient, a 30-year-old Korean man, was admitted because of nausea and vomiting associated with diffuse abdominal pain, headache, nonproductive cough, myalgias, and temperatures as high as 38.3°C (101°F), all of three days' duration. Four days before admission the patient had returned from a vacation to Korea. He had trav-

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
ELISA = enzyme-linked immunosorbent assay
Ig = immunoglobulin

eled during the month of December 1993 and had stayed in rural inns where he at times slept on the floor.

On physical examination the patient was orthostatic to pulse only. He had mildly injected sclerae, an erythematous oropharynx, and a nondistended abdomen that was soft but diffusely tender only on palpation. A stool specimen obtained on rectal examination was brown and tested positive for occult blood. A nonpalpable petechial rash was present over the patient's legs and back.

Initial laboratory studies showed a leukocyte count of 46.8×10^9 cells per liter with a manual differential of 0.16 neutrophils, 0.44 bands, 0.08 lymphocytes, 0.05 monocytes, 0.01 eosinophils, 0.01 basophils, 0.02 metamyelocytes, 0.01 progranulocytes, and 0.22 blast forms. The platelet count was 37×10^9 per liter. The hematocrit was 0.59. Urinalysis revealed a specific gravity of 1.022, pH 5.0, 3+ protein, 1+ ketones, 0 to 3 leukocytes and erythrocytes, greater than 50 hyaline casts, and occasional granular casts with rare erythrocyte inclusions. The other abnormal admission laboratory values are shown in Table 1. Cultures of blood and urine were obtained, and a regimen of intravenous cefotetan was started empirically.

A closer review of the peripheral blood smear showed that the cells originally thought to represent blast forms were instead atypical lymphocytes. A Monospot slide test was negative for infectious mononucleosis. A test for hepatitis B surface antigen was positive. On hospital day 2 after intravenous hydration, the leukocyte count was 49.3×10^9 per liter, the hematocrit was 0.489, and the platelet count was 52×10^9 per liter. The serum creatinine level remained elevated at 210 μmol per liter (2.4 mg per dl). The patient continued to be afebrile and normotensive.

TABLE 1.—*Abnormal Serum Biochemistry Values on Admission*

Test, Serum	Results: SI Units	Results: (Conventional Units)
Sodium, mmol/liter (mEq/liter)	125	(125)
Urea nitrogen, mmol/liter (mg/dl)	21.1	(59)
Creatinine, μmol/liter (mg/dl)	260	(2.9)
Alanine aminotransferase, U/liter (units/liter)	109	(109)
Aspartate aminotransferase, U/liter (units/liter)	119	(119)
Lactate dehydrogenase, U/liter (units/liter)	1,500	(1,500)
Creatine kinase, U/liter (units/liter)	275	(275)
Calcium, mmol/liter (mg/dl)	1.92	(7.7)
Magnesium, mmol/liter (mg/dl)	0.6	(1.4)
Amylase, U/liter (units/liter)	320	(320)

SI = Système International

On hospital day 3 periorbital puffiness was noted on physical examination, along with bibasilar rales. An abdominal ultrasonogram showed small pleural effusions of both lungs. Furosemide was administered intravenously with subsequent moderate diuresis.

The patient's temperature went up to 38.8°C (102°F) on hospital day 4. The platelet count had risen to 135×10^9 per liter and the leukocyte count had come down to 22.8×10^9 per liter. The serum creatinine level rose to 410 μmol per liter (4.6 mg per dl). Despite escalating doses of diuretics, the urine output fell to below 500 ml per 24 hours, and the patient began to have shortness of breath. Worsening rales were noted on pulmonary examination, and the results of a chest x-ray film were consistent with pulmonary edema. Arterial blood gas determinations with the patient breathing room air revealed a pH of 7.39, Po_2 of 42 mm of mercury, Pco_2 of 29 mm of mercury, and a bicarbonate level of 17.5 mmol per liter (17.5 mEq per liter). The patient was placed on supplemental oxygen therapy. A cross-referenced MEDLINE search on thrombocytopenia, acute renal failure, and Korea suggested the diagnosis of hemorrhagic fever with renal syndrome. A serum specimen for serologic testing of antibodies to hantavirus was sent to the Centers for Disease Control and Prevention (CDC).

On hospital day 6 the patient's urine output increased to more than 3 liters per 24 hours in the absence of diuretic administration. The serum creatinine level decreased to 320 μmol per liter (3.7 mg per dl). The following morning the patient left the hospital against medical advice. That afternoon the CDC reported that the patient's serum contained immunoglobulin (Ig) M antibody against hantavirus.

At outpatient follow-up 11 days later, the patient had no complaints, his blood urea nitrogen level was 3.6 mmol per liter (10 mg per dl), and his serum creatinine level was 110 μmol per liter (1.3 mg per dl).

Discussion

During the Korean War a syndrome of fever and acute renal insufficiency associated with thrombocytopenia and hemorrhagic manifestations of varying degree developed in more than 2,000 United Nations troops.[5] This clinical spectrum was labeled Korean hemorrhagic fever and was compared with similar syndromes reported in Scandinavian countries (nephropathia epidemica) and in China and Japan (epidemic hemorrhagic fever). It was not until 1978 that the causative agent of Korean hemorrhagic fever, Hantaan virus, was first isolated from lung tissue of a striped field mouse (*Apodemus agrarius*).[6] Subsequent research revealed that the similar clinical syndromes were caused by closely related viruses.[7,8] In 1982 a World Health Organization working group recommended that these diseases be referred to as hemorrhagic fever with renal syndrome.[9] The initial three viral strains shown to cause human disease were grouped into the *Hantavirus*

genus of the Bunyaviridae family.[2] Further serologic study has established additional hantavirus serotypes,[10] each serotype characterized by a prototypical mammalian vector, geographic distribution, and disease severity (Table 2).[11-13]

Humans become infected with hantavirus through inhalation or direct contact with virus found in rodent excreta. Hantavirus infection in rodents is unique in that despite the presence of neutralizing antibody, infectious virus continues to be secreted in urine, saliva, and feces without any detrimental effect on the host rodent.[14] Human excretion of virus is minimal, and transmission between humans has never been reported.[1] Possible hantavirus vector-rodents are widespread. Serologic evidence of hantavirus infection has been demonstrated in 81 species of animals in more than 50 countries on all continents except Antarctica.[2] In the United States the highest prevalence of hantavirus-infected rats has been found in Baltimore, Maryland (34% to 74%); New Orleans, Louisiana (31% to 41%); the Hawaiian islands (6% to 18%); and Philadelphia, Pennsylvania (12%).[10] Seroprevalence surveys of rodents in California, Alaska, Colorado, New Mexico, and Utah have found a prevalence of hantavirus infection as high as 21%.[10] Testing of rodents captured in and around homes of case-patients in the recent southwestern United States outbreak of acute adult respiratory distress syndrome revealed 32 of 107 (30%) deer mice (*Peromyscus maniculatus*) to be positive for hantavirus infection.[15] Despite the widespread distribution of infected rodents, no indigenously acquired case of hantavirus disease had been reported in the United States before the recent recognition of hantavirus-related severe respiratory illness (hantavirus pulmonary syndrome) in the southwestern United States.

The incubation period for hemorrhagic fever wth renal syndrome is generally two to three weeks, with a range of 4 to 42 days. Early symptoms include high fever, flushing of the face, myalgias, conjunctival and pharyngeal injection, frontal headache, and a petechial rash, with subsequent development of nausea and vomiting, severe abdominal pain, and back pain with costovertebral angle tenderness.[3,5,16] Hiccups and severe thirst are common.[5] The classic syndrome has five clinical stages: febrile, hypotensive, oliguric, diuretic, and convalescent. Distinct stages often are not recognizable, especially with mild to moderate disease. The febrile stage can last as long as five days. Shock and oliguric phases often overlap and last an average of six days (range 2 to 12 days). Convalescence can take months, with persistent proteinuria and defects in urine-concentrating ability.[17]

Laboratory findings invariably include proteinuria, often pronounced. As a rule, azotemia is present as well, but it may be absent in mild cases.[16] Leukocyte counts are substantially elevated, especially in Hantaan strain infections. Atypical lymphocytes on a peripheral smear are seen in more than 93% of cases, and the simultaneous presence of immature granulocytes and giant platelets supports the diagnosis of hemorrhagic fever with renal syndrome.[5]

Our patient had transient hypoxemia with radiographic evidence of pulmonary edema on days 7 and 8 of his illness. This clinical finding is particularly interesting in light of the recent descriptions of hantavirus pulmonary syndrome in the United States. Vascular endothelial cell injury followed by increased capillary permeability is thought to result in the observed pulmonary complications.[18]

TABLE 2.—*Hantavirus Genus Varieties*

Viral Serotype (Year Discovered)	*Acute Disease Severity*	*Seasonality*	*Prototypical Vector*	*Documented Distribution*
Hantaan (1976)	20% severe; 50% moderate; 30% mild	Late fall or early winter; spring or early summer	Striped field mouse (*Apodemus agrarius*)	Asia: China, Korea (rural)
Seoul (1982)	Mild to moderate; severe on occasion; hepatitis	None	Domestic rat (*Rattus rattus, Rattus norvegicus*)	Worldwide (urban)
Puumula (1984)	Less severe	Late fall or early winter; mid to late summer	Bank vole (*Clethrionomys glariolus*)	Scandinavia, Russia, Europe
Prospect Hill (1982)	Asymptomatic*	--	Meadow vole (*Microtus pennsylvanicus*)	Maryland, Minnesota†
Leakey (1988)	Severe‡	--	House mouse (*Mus musculus*)	Texas, Maryland, Minnesota†
Porogia (1987)§	Severe	?	?	Greece†
Belgrade (1992)‖	Severe	?	Yellow-necked mouse (*Apodemus flavicollis*)?	Balkan region†
Muerto Canyon (1993)	Severe; adult respiratory distress syndrome	Single outbreak in spring 1993	Deer mouse (*Peromyscus maniculatus*)	Concentration in southwestern United States†

* No acute symptoms documented to date.
† Actual event of geographic distribution unknown.
‡ A single case of serologic evidence of Leakey virus infection has been reported in a patient with severe hemorrhagic illness and renal insufficiency (Baek et al[11]).
§ Proposed name for hantavirus identified in a severely ill patient with hemorrhagic fever with renal syndrome in Greece that showed a unique serologic pattern relative to Hantaan, Seoul, and Puumula viruses (Antoniades et al[12]).
‖ Hantavirus strain is identified in severely ill patients with hemorrhagic fever with renal syndrome in the Balkan region (Gligic et al[13]).

The protean and nonspecific manifestations of hemorrhagic fever with renal syndrome, especially in mild to moderate cases, make diagnosing this disease on clinical grounds difficult. Important clinical clues are fever, frontal headache, and myalgias in conjunction with flushing and conjunctival or pharyngeal injection. The additional presence of hypotension, marked proteinuria, thrombocytopenia, and acute renal failure in a person with a travel history to Russia, Asia, or Scandinavia, particularly in late autumn or early winter, strongly suggests the diagnosis. A history of exposure to rodents provides collaborating evidence.

The various diseases that patients with this illness have been misdiagnosed as having include leptospirosis, scrub typhus, bacterial sepsis, dengue fever, viral hepatitis, acute surgical abdomen, and influenza. Uremia related to thrombocytopenic thrombotic purpura or the hemolytic-uremic syndrome should also be considered in the differential diagnosis. Antibiotics and nonsteroidal anti-inflammatory agents given empirically to febrile patients can result in acute renal failure due to interstitial nephritis and present a clinical syndrome suggestive of hemorrhagic fever with renal syndrome without thrombocytopenia or hypotension. Jaundice is rare in this disease, and its presence is indicative of leptospirosis or viral hepatitis. Similarly, a maculopapular rash is more consistent with leptospirosis or scrub typhus.

The current diagnostic method of choice is the detection of IgM antibodies against hantaviruses using enzyme-linked immunosorbent assay (ELISA). Testing is available through the CDC Special Pathogens Branch of the Division of Viral and Rickettsial Diseases. Although the ELISA is not able to determine the specific strain of infecting virus, it is a specific and sensitive technique for detecting acute hantavirus infection and is positive in most patients by day 3 of the febrile stage.[19] Specific viral strains can be determined by plaque-reducing neutralization assays.

Rapidly diagnosing this illness is important because a prospective, randomized, double-blind, placebo-controlled clinical trial in China has demonstrated a sevenfold decrease in mortality with the early use (within 6 days of the onset of fever) of intravenous ribavirin. The primary effect appears to be a reduction in the risk of entering the oliguric phase.[20] Intravenous ribavirin is not currently licensed for use in the United States, but has been made available through an investigational-new-drug protocol to treat patients with hantavirus pulmonary syndrome.

Severe hemorrhagic fever with renal syndrome has a mortality of 5% to 10%. As of December 31, 1993, a mortality of 60% had been reported in 53 confirmed cases of hantavirus pulmonary syndrome throughout the United States.[21] In mild to moderate cases of hantavirus disease, supportive care usually leads to full recovery, but recent data suggest that subclinical infections in the United States may lead to long-term sequelae. Seropositive inpatients in Baltimore were more likely than matched controls to have end-stage renal disease, hypertension, and stroke.[22]

The results of preliminary trials of inactivated vaccines against this disease have been encouraging,[23] and vaccinia-vectored vaccines are under development.[24] The best preventive measure at this time appears to be to avoid activities that would result in close contact with rodents or their excreta.

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