Malaria Infection in Transplant Recipient

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A case of P. malariae infection occurring in a kidney transplant recipient is reported. The diagnosis was delayed because of atypical clinical presentation secondary to altered immune response. Serologic tests for antimalarial antibody are not reliable and diagnosis is established by visualization of the parasites in the peripheral blood smear. We can only guess what role this infection played in rejection of the transplant and whether earlier diagnosis and treatment would have saved it.

Infection remains the major cause of morbidity and death among renal transplant patients. These patients have altered defense mechanisms based on their basic renal disease and uremia, their generally debilitated state, and the purposive immunosuppressive therapy routinely given to prevent transplant rejection. They are thereby rendered highly susceptible, not only to the usual pathogens, but to more serious infections such as gram-negative bacteria, nocardia, candida, asperigillus, histoplasma, cytomegalovirus, herpes virus, and Pneumocystis carinii.[1] This report adds malaria to the growing list of infectious agents affecting the transplant recipient.

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Case Report

A 28-year-old Nigerian male was first admitted to Howard University Hospital on July 7, 1975, for severe hypertension and azotemia. His illness started a year prior to admission with progressive shortness of breath and dizziness. He was found to have hypertension, leg edema, and evidence of renal disease and was treated with antihypertensive medications. Past medical history revealed smallpox at the age of nine years. He was found to be healthy when examined for entry to the United States in 1971, and while an engineering student in Leningrad, USSR, in 1970. He had no medical problems.

On admission, the patient had a blood pressure of 220/130 mm Hg. Ophthalmoscopic examination revealed arteriolar narrowing with arteriovenous nicking bilaterally but no hemorrhages, exudates, or papilledema. The physical examination was otherwise unremarkable. The significant laboratory data were: Blood urea nitrogen (BUN) level 130 mg/100 ml, serum creatinine level 16 mg/100 ml, and creatinine clearance rate of 3.1 ml/minute. An arteriovenous shunt was inserted and he was placed on chronic hemodialysis. However, even with ultrafiltration, his blood pressure was difficult to control. Bilateral nephrectomy and splenectomy were done on September 12, 1975, partly to control hypertension, and partly in preparation for renal transplantation. Pathological examination of the removed kidneys showed severe arterio and arteriolar nephrosclerosis. Histologic examination of the spleen revealed no pathological lesions and, in particular, nothing to suggest malaria.

On October 23, 1975, the patient received an ABO compatible, 2 HLA antigen (one haplo type) matched kidney from an 18-year-old sibling whose leukocyte crossmatch was negative prior to kidney transplant. The recipient received the standard immunosuppressive regimen used at Howard University Hospital, namely, goat antilymphocyte globulin, azathi-

oprine, and prednisone. The transplant and post-transplant course was uneventful and 15 days after transplantation the patient was discharged with a hematocrit of 33, white blood cell count of 9,500, urine output about 1,500 ml/day, normal serum electrolytes, BUN 17 mg/100 ml, and serum creatinine 1.5 mg/100 ml. Following discharge he was seen as an outpatient three times a week. Two weeks later, on November 26, 1975, he was readmitted because of a fever of 103F, chills, and a dry cough. He was now oliguric and his BUN and serum creatinine levels were 41 mg/100 ml and 3.0 mg/100 ml, respectively. Antirejection therapy, consisting of irradiation of the transplanted kidney, intravenous solumedrol, increased prednisone, and decreased azathioprine was instituted. Nystatin was also given as prophylaxis against oral candidiasis. Within one week of this treatment, his BUN and creatinine fell and his fever temporarily declined, but herpes labialis lesions were noted on the right cheek.

On December 4, 1975, malarial parasites were incidentally identified in his blood and primaquine therapy started. In spite of this, his condition deteriorated and on December 8, 1975, he was readmitted with dyspnea, chills, and fever up to 104F. Because of an eight-pound weight gain, he was thought to have suffered an exacerbation of the acute rejection. Antirejection therapy was reinstituted and he was dialysed. However, fever persisted, the herpes labialis extended and became superinfected, and his general clinical condition deteriorated. Thus, although his renal function had stabilized, it was thought prudent to sacrifice the transplant on December 18, 1975. Blood cultures two days later revealed Pseudomonas septicemia which was successfully treated with gentamycin. The patient did well thereafter and was discharged on January 2, 1976. Plasmodium malariae forms were seen on two peripheral blood smears. Malarial indirect immunofluorescent tests on his serum revealed a titer of 1:64 against Plasmodium falciparum, none against P vivax or P malariae. A repeat study three months later revealed a titer of 1:256 against P falciparum, none against P vivax or P malariae. His brother's serum revealed a titer of 1:4,096 for P falciparum, 1:256 for P malariae, and 1:64 for P vivax.

The pathological picture of the transplanted kidney revealed minimal evidence of rejection.

Discussion

This report describes an uncommon infection occurring in an immunosuppressed and splenectomized host. The presenting chills and fever were initially thought to be due to either acute rejection or to one of the usual post-transplant infections. When rejection occurs within 90 days after renal transplantation, most of the patients become azotemic and oliguric and develop a temperature higher than 101F. Herpes simplex or cytomegalovirus infection has invariably been associated with this rejection either as the trigger, or at least, as an intercurrent problem.[2] Rejection episodes have been reversed in most such patients.

As it had been assumed that the patient was having a routine injection crisis, the finding of malarial parasites on routine peripheral blood smear was surprising. Was malaria the trigger for this rejection, or was it a combination of a virus infection and malaria? Had the apparent delay in diagnosis and institution of antimalarial therapy contributed to the loss of the transplant? These questions remain largely unanswered.

Furthermore, it is confusing that the morphology of the parasites suggested P malariae which affects the kidney mainly by causing a nephrotic syndrome, while the serology revealed titers only against P falciparum. Falciparum malaria is a well known cause of acute renal failure usually on the basis of massive hemolysis, dehydration, hypotension, and intravascular coagulation.[3] However, the histology of the nephrectomized allograft kidney, in this case, was consistent with minimal rejection and not with renal failure secondary to severe malaria. Delay in diagnosis of malaria is not unusual and happens even under the best of circumstances. In this case, perhaps as a result of altered defense mechanisms induced by both renal failure and by immunosuppressive drugs, including steroids, there was no clue from the periodicity of fever and chills. As sometimes happens, the degree of parasitemia may have been low and therefore it was hard to demonstrate the diagnostic forms on routine peripheral blood smears. Physical examination is frequently not helpful, for apart from the fact that this patient had a splenectomy, splenomegaly is present only in 50 percent of cases.[4] Ordinarily, a normal leukocyte count or slight leukopenia of malaria may be helpful in differentiating this disease from a febrile bacterial illness. This clue is sometimes neutralized in the immunosuppressed subject.

A high index of suspicion is necessary if the diagnosis of malaria is not to be missed. Most cases reported in the United States have been among military personnel, with a rather high incidence during the Vietnam War.[5] Those civilians who contract the disease usually have a history of foreign travel or are themselves visitors from areas of the world in which malaria is endemic. Some of these may have latent infection with the potential for clinical relapse and for serving as a reservoir of the disease. It is possible then for an individual in the United States to contract malaria without ever leaving the country. Seven cases of malaria were acquired within the United States in 1972, and two in 1973.[6] In 1972, three were transmitted by blood transfusion, and two by needle-sharing associated with illicit use of heroin. One was transmitted congenitally, probably transplacentally from an infected mother.[7]

The source of infection in our patient is unknown. It could represent reactivation of a dormant or endogenous infection acquired prior to immunosuppression. It could be an exogenous infection transmitted during one of the several blood transfusions during dialysis and/or surgery. It could also have come from an infected donor kidney.

Since the liver phase of P malariae, unlike that of P falciparum, may persist for a prolonged period of time, we suspect that our patient had latent P malariae infection which became manifest following immunosuppression and/or splenectomy. Immunosuppression due to viral infection may also enhance malarial infection. Salaman[8] noted that healthy virus-infected mice when infected with malaria died of fulminant parasitemic anemia in contrast to non-viral infected mice. The absence of a measureable titer for P malariae is most likely secondary to immunosuppression. The appearance of significant titer to P falciparum three months later when the patient was no longer taking immunosuppressive agents and the fact that this titer is infinitely lower than his

brother's, support this possibility.

Shute[9] raised concern regarding susceptibility of splenectomized patients to malaria. Research on apes and monkeys has shown that when these animals have acquired immunity to malaria, they can be reinfected with the same strain of the same species of parasites if, before reinfection, the spleen is removed. It has also been proved that chimpanzees, which normally are resistant to human P vivax infections, develop severe parasitemia if the spleen is removed prior to infection. Shute cautioned humans who have had their spleens removed to avoid traveling to endemic areas.

Malaria, therefore, should be included in the differential diagnosis of fever and chills in immunosuppressed patients. Examination of peripheral blood smears should be done routinely, although the parasites may be mistaken for platelets or artifacts by the unsuspecting. The key is to maintain a high index of suspicion.

Serologic test for antimalarial antibody, either by indirect hemagglutination or immunofluorescence, may be helpful. A high antibody titer suggests active or recent infection while a low titer may only reflect infection at some time in the past. The history of travel in an endemic area may be an important clue to the diagnosis. However, since transmission may occur through blood transfusion, transplacentally, or via mosquito bites, a negative history of travel should not eliminate this possibility.

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Fetal Alcohol Syndrome

Excessive use of alcohol by women during pregnancy can result in a characteristic pattern of congenital abnormalities, termed the fetal alcohol syndrome. Both prenatal-onset and postnatal developmental and performance deficiencies are present. First recognized in this country in 1972, the syndrome consists of behavioral, craniofacial, limb, and neurological anomalies and, in nearly 50 percent of reported cases, cardiac septal defects, genital abnormalities, and hemangiomas. Primary anomalies of the head and face include microcephaly, short fissures of the eyelids, midfacial defects, and a flattened elongated vertical groove in the upper lip. Malformations of the hands include abnormal palmar creases and joined, deviated, or permanently flexed fingers and toes. The IQs of affected individuals average 35-40 points below normal.

Studies in animals corroborate observations that alcohol is a potent teratogen which also increases the incidence of stillbirths, resorptions, and spontaneous abortions. The latter observations in animals are particularly important because of the inherent difficulties of assessing risk factors related to spontaneous abortions in humans.

The risk and extent of abnormalities in both humans and animals appear to be dose related; both increase with increase in maternal alcohol intake. Pregnant women should definitely refrain from "binge" drinking. High blood alcohol levels may produce malformations during the first trimester and growth retardation during the third trimester. Although the latter is yet to be fully confirmed in humans, in one recent study, 32 percent of infants born to heavy drinkers demonstrated congenital anomalies, compared with nine percent in the abstinent and 14 percent in moderate drinkers. Microcephaly was frequently observed.

Alcohol during pregnancy is the unequivocal factor when the full pattern of fetal alcohol syndrome is present in humans. But in cases where all the characteristics are not present, the correlation between alcohol intake and its adverse effects is complicated by factors such as nutrition, smoking, caffeine, certain other drugs, and various environmental agents. (*FDA Drug Bulletin*, September-October, 1977).