Primary reticulum cell sarcoma of the brain in a renal transplantation recipient

Case report

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A case of primary reticulum cell sarcoma of the brain (microgliomatosis) is reported in a kidney transplant recipient treated with immunosuppressants, the second such case seen at this institution. Hypotheses for the mechanism of lymphoma development in this situation are reviewed, and the remarkable predilection for the brain is pointed out.

KEY WORDS renal transplantation immunosuppressive therapy primary reticulum cell sarcoma brain tumor microgliomatosis

SINCE the first report by Doak, et al., 2 in 1968, 25 cases of malignant lymphomas have been collected by the Human Renal Transplant Registry in patients who had undergone renal transplantation and received immunosuppressive therapy.4 Fourteen cases occurred in the central nervous system; in 11 of these the brain was the only organ involved. One additional case involved the meninges and the underlying cerebellum, which was the only site of tumor.11 The surprisingly high incidence of cerebral lymphoma in patients receiving immunosuppressive therapy and the possible mechanisms involved have been discussed by previous authors.10,18 Experimental work has also repeatedly confirmed the relationship between immunosuppressive agents, with or without transplantation, and lymphomas.1,3,6,16 The prompt diagnosis of cerebral lymphomas may be of some importance, since Schneck and Penn9 have reported the successful removal of the tumor in one patient; in general, however, the prognosis is considered to be extremely poor.9

This communication describes a case of reticulum cell sarcoma of the brain in a patient with renal transplantation who received immunosuppressive therapy, and reviews the possible mechanism of this predilection of reticulum cell sarcoma for the brain in this particular situation.

Case Report

On October 28, 1969, a renal cadaveric homotransplantation (B match) was performed on this 38-year-old man with severe chronic glomerulonephritis. About 14 days following the transplantation, signs of acute
rejection were noted and the patient was treated with azathioprine (125 mg/day), prednisolone (100 mg/day), irradiation to the kidney (total 600 rads), and horse antilymphocytic serum (5 ml/day) which was discontinued shortly thereafter because of an anaphylactic reaction. Good improvement in renal function was noted, with a creatinine clearance of 37.4 cc. He was discharged on December 24, with oral azathioprine 100 mg and prednisolone 16 mg daily. Six weeks later he was readmitted and a left epididymoorchietomy was done for recurrent epididymitis with abscess formation. In February, 1970, he returned with abnormal liver enzymes, jaundice, and a positive serum hepatitis antigen. A diagnosis of serum hepatitis was made. The enzymes and bilirubin returned to normal after a few days of hospitalization, and the patient was discharged doing well.

On May 23, 1970, 7 months post transplantation, he was readmitted to The New York Hospital with fever and cachexia. Chest films revealed infiltration of the right lung which failed to respond to the antibiotic therapy and eventually became bilateral and confluent. On May 26, the patient suddenly developed a series of convulsions that characteristically started in the left arm but progressed to generalized seizures. These were brought under control with Valium and Dilantin. A brain abscess was suspected but the electroencephalogram was diffusely abnormal with no evidence of focal lesions, and the tracing was interpreted as showing bilateral cerebral dysfunction. A brain scan and right carotid angiogram were negative. The patient remained disoriented and developed gastrointestinal bleeding and septicemia with blood cultures positive for yeast forms and gram-negative bacilli. He died on July 16, 1970.

Postmortem Examination. The lungs weighed 1250 gm together and had bilateral confluent bronchopneumonia with an abscess in the right upper lobe. Extensive fungal peritonitis (Candida albicans) was present with typical candida ulcers in the esophagus and stomach. The liver showed chronic active hepatitis of moderate severity. Intranuclear and intracytoplasmic inclusions typical for cytomegalovirus were found in the lining cells of the pulmonary alveoli and salivary glands, but not in the kidneys or the brain. Characteristic cytopathic effects of cytomegalovirus were reported after the death of the patient on a urine culture taken several weeks antemortem.

The recipient’s kidneys were bilaterally contracted and finely granular on the surface, weighing 90 gm together. Microscopically, nearly all glomeruli were completely hyalinized. The interstitium showed diffuse fibrosis, and tubules were atrophic. The lumina of the blood vessels were markedly narrowed by intimal thickening. In the renal homograft (160 gm) small and large arteries were narrowed by moderate to marked intimal thickening. The fibrous tissue within the interstitium was focally increased, and tubules in these areas were atrophic. The glomerular capillary walls and mesangial areas were thickened. Only occasional foci of round cell infiltration were present in the interstitium. These changes were interpreted as consistent with chronic rejection.

Neuropathological Findings. The brain weighed 1350 gm and showed right uncal notching and prominence of the gyri over the right frontoparietal lobe. Coronal sections of the right posterior frontal lobe revealed an ill-defined area of greenish yellow, soft, partially necrotic tissue which mainly involved the subcortical white matter (Fig. 1). The tumor extended from the level of the optic chiasm to that of the lateral geniculate body. The surrounding brain tissue was moderately edematous but otherwise the remainder of the brain appeared normal grossly. Sections taken through the tumor showed sheets of small, pleomorphic cells with vesicular nuclei, prominent nucleoli, and an ill-defined, scanty,
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pale pink cytoplasm (Fig. 2 left). These tumor cells infiltrated the underlying brain substance diffusely but with a predominant tendency to a perivascular arrangement (Fig. 2 right). There were large areas of necrosis in the tumor. The findings were typical of reticulum cell sarcoma (microgliomatosis).

Careful microscopic examination of the rest of the brain showed no evidence of either viral or fungal infection. Alzheimer type II astrocytes were noted, especially in the basal ganglia. Careful examination of the lymph nodes, spleen, bone marrow, and viscera failed to show evidence of tumor infiltration.

Discussion

There have been 25 cases of lymphomas reported in patients who have undergone renal transplantation and have received immunosuppressive therapy. The incidence has been estimated to be 2.2 per 1000 per year in transplant recipients, which is 350 times greater than in a similar age group in the general population.

When primary reticulum cell sarcoma of the brain (microgliomatosis) is considered separately, the remarkable increase of its incidence after transplantation becomes even more apparent. Primary lymphoma of the brain is a rare tumor in the general population; only 12 cases were recognized among 25,200 autopsies performed at the Massachusetts General Hospital, an estimated incidence of less than 0.05%.

Our experience at The New York Hospital indicates an increased incidence of primary reticulum cell sarcoma of the brain in immunosuppressed renal transplant patients. During the last 5 years no cases of this disorder have been seen at autopsy in nonrenal transplant patients (over 2500 autopsies). A single case has been seen in surgical pathology material from an otherwise normal individual during the same interval. Yet ours is the second case encountered at postmortem examination during the same period among the immunosuppressed renal transplant group (157 patients); a previous case has been reported in part by Schneck and Penn.

Experimentally, lymphomas have been developed or enhanced in mice by immunosuppressive agents, notably by antilymphocytic globulin and azathioprine. When antigenic stimulation is added to immunosuppressive therapy, the tumor induction capacity of the latter is greatly enhanced. Many have remarked on the infrequency of lymphoma in patients who have received long-term immunosuppressive therapy for disease states other than transplantation. These observations have suggested to previous authors that immunosuppressive therapy in the presence of a

Fig. 2. Left: Photomicrograph of tumor demonstrating sheets of pleomorphic cells typical of reticulum cell sarcoma. H & E, × 384. Right: Photomicrograph showing the frequent perivascular arrangement of tumor cells. H & E, × 120.
continuous antigenic stimulation (transplanted kidney) is causally related to lymphoma in the human being.\textsuperscript{2,7,10,11,13}

The underlying mechanism for this relationship is not known, but proposed theories include the following: 1) sustained antigenic stimulation by the homograft may lead to the increased production of neoplastic cells; 2) immunosuppressants may inhibit the normal defense mechanism against lymphoma; 3) immunosuppressants may permit the emergence of a tumor virus; 4) immunosuppressants may cause chromosome breakage, inducing malignancy.\textsuperscript{10} If these mechanisms, singly or in combination, are assumed to be responsible for lymphoma development in transplant recipients, why do these lesions occur so frequently in the brain?

Schneck and Penn\textsuperscript{10} suggest that in most of the transplant recipients, immune surveillance outside the brain may remain sufficient to prevent the development of generalized lymphomas. Even though the most important defense mechanism against tumor has been widely accepted as being cell-mediated, there has been growing evidence that humoral factors play an important role.\textsuperscript{5,12,15} While cellular immunity is markedly reduced due to immunosuppressive therapy, humoral factors may still be at work outside the brain, at least at an earlier stage; however, because of the blood-brain barrier, the brain may be excluded from these humoral factors. Schneck and Penn\textsuperscript{10} suggest that in most of the transplant recipients, immune surveillance outside the brain may remain sufficient to prevent the development of generalized lymphomas. Even though the most important defense mechanism against tumor has been widely accepted as being cell-mediated, there has been growing evidence that humoral factors play an important role.\textsuperscript{5,12,15} While cellular immunity is markedly reduced due to immunosuppressive therapy, humoral factors may still be at work outside the brain, at least at an earlier stage; however, because of the blood-brain barrier, the brain may be excluded from these humoral factors. The combination of a possibly weak inherent response of the brain to antigenic stimulation (perhaps due to lack of lymphatics) together with the already profound reduction of generalized cellular immunity caused by immunosuppressants may contribute to the increased susceptibility.

Smithers and Field\textsuperscript{13} suggest that the blood-brain barrier may also exclude immunosuppressants which are chemotherapeutic, and which may be important in preventing lymphoma development elsewhere in the body.

It has also been suggested that these intracranial lymphomas may all have originated at unknown primary sites outside the brain.\textsuperscript{10} However, in one series of over 1500 lymphocytes, only one intracerebral metastasis was found;\textsuperscript{14} in another series, two of 121 showed cerebral lesions.\textsuperscript{8} Thus, it is rather difficult to assume that most intracerebral lymphomas in transplant recipients are metastatic, when 11 out of 25 lymphomas in this population were present only in the brain.

While in transplant patients most of the lymphomas occurred in the brain, no gliomas have been reported in this population. This may be related to oncogenic virus infection,\textsuperscript{10} or to the fact that lymphoma is a tumor of the immune system which is actively challenged in this group of patients.

References

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