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Transplantation

BRIEF COMMUNICATIONS

EXPRESSIVE DYSPHASIA POSSIBLY RELATED TO FK506 IN TWO LIVER TRANSPLANT RECIPIENTS¹

The principal side effects of the new immunosuppressive drug FK506 have been low-grade nephrotoxicity, a mild diabetogenic effect, and annoying but relatively minor manifestations of neurotoxicity (1). The neurotoxic symptoms have included tremors, paresthesias, insomnia, headaches, increased visual sensitivity to light, nightmares, a sense of racing, and mood changes. Such complaints, which are similar to those caused by cyclosporine, have provided a much-needed means of dose adjustment (1). However, we report here 2 examples of reversible expressive dysphasia that may have been caused by FK506 since it was reversed by dose reduction.

Both patients were treated from the time of liver transplantation with FK506, starting with an initial intravenous dose of 0.15 mg/kg FK506 intraoperatively. Subsequent intravenous doses of 0.075 mg/kg were given every 12 hr, until the patients were able to take oral medications. At this time, 0.15 mg/kg FK506 was given orally every 12 hours. Methylprednisolone was started at 200 mg on day 1 and reduced by 40 mg steps/day to 20 mg on day 6.

A 43-year-old man with end-stage postnecrotic cirrhosis (liver weight 1400 g) secondary to hepatitis B did not have disabling encephalopathy preoperatively. He had an uncomplicated orthotopic liver transplantation, with a 3000 ml blood loss. He was discharged from the ICU after 3 days. On day 12, he was noted to have slurring of speech. He complained of numbness and tingling in his feet and also that his head was "racing." There was no arterial hypertension, nor any elevation of BUN or creatinine. Serum electrolytes were never abnormal, intraoperatively or later. The neurologic examination revealed an expressive dysphasia with slight tremors of the extremities. Fundoscopic findings, magnetic resonance imaging of the brain, and the spinal fluid were normal. A cerebral CT scan showed mild cortical atrophy, a finding that had been noted in the preoperative CT scan. An EEG showed generalized slowing. The neurologic symptoms gradually resolved after an FK506 dose reduction. Despite a minor rejection episode, he improved steadily, and by the time of discharge, 25 days postoperatively, the speech defect was barely perceptible. He is neurologically normal 4 months postoperatively on FK506 doses of 0.09 mg/kg/day (less than one-third of early postoperative oral dose) and 10 mg/day prednisone.

A 38-year-old woman with chronic HBV hepatitis and grade III encephalopathy had an uncomplicated urgent liver transplantation. Preoperatively, she was agitated and disoriented. Later, she became drowsy, disoriented, and bradykinetic. Immunosuppression was as in case 1. Postoperatively, she required

prolonged ventilatory support and developed nonoliguric renal insufficiency—the serum creatinine rising from normal preoperatively to a peak of 5.3 mg/dl. The intravenous dose of FK506 was decreased to .035 mg/kg/b.i.d. When the endotracheal tube was removed on day 6, she was noted to have an expressive speech deficit. Talking required a severe effort and there were occasional paraphasias. Her comprehension appeared to be normal, and repetitive speech was easier than spontaneous expression. A small subcortical left hemispheric stroke was suspected. However, a CT brain scan on days 6 and 12, carotid doppler examination, and echocardiogram (to rule out valve vegetations as an embolic source) were normal. The cerebrospinal fluid was normal. Her subsequent course was stormy and included *Pseudomonas* pneumonia, abdominal reoperation to remove a subhepatic hematoma, acute renal failure requiring 7 hemodialyses, tracheostomy, and CMV gastritis. The FK506 doses were intermittently stopped during this time and eventually resumed with oral doses of .07 mg/kg/day (about a quarter of the usual dose).

When her tracheostomy was capped on day 41, she was noted still to have slurring of speech. Magnetic resonance imaging on the 41st postoperative day showed areas of demyelination in the pons (Fig. 1). The oral dose of .07 mg/kg FK506 per day was maintained. The expressive dysphasia slowly improved and she was discharged on the 56th postoperative day. Her speech abnormalities completely resolved by postoperative day 90. She has never had a rejection. Maintenance immunosuppression 5 months postoperatively is with 0.06 mg/kg/day FK506 without steroids, which were stopped on the 16th postoperative day.

Pathologic changes can frequently be found in the central nervous system of patients who die of chronic liver disease (2). The same abnormalities have been seen at autopsy after unsuccessful transplantation under azathioprine and cyclosporine regimens (3, 4). In order of frequency, these include Alzheimer type II changes in the glial tissue, depletion of the myelin in the pons (central pontine myelinolysis) or elsewhere in the brain stem or higher brain (extrapontine myelinolysis), and cortical atrophy.

The neurologic syndromes have included prolonged obtundation or disorientation, flaccid quadriplegia, pseudobulbar palsy, expressive dysphasia, akinetic mutism, neuroophthalmologic abnormalities, convulsions, and coma (3, 4). Similar Alzheimer and myelinolytic changes can be produced reliably in rats by surgical portacaval anastomosis, even though the animals may appear well clinically (5). Thus, vulnerability from underlying neuropathologic abnormalities of the central nervous system during the stressful period of liver transplantation is the background against which the role of any single factor, including drugs, must be evaluated in the event of a neurologic

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FIGURE 1. NMR in patient 2 on the 41st postoperative day. Note the bright pontine lesion (arrow), which was thought to be an area of demyelination.

complication. The possible aggravating role of overly aggressive electrolyte correction has been emphasized by many workers, as summarized by Wszolek et al. (6).

Nevertheless, the possible neurologic complications of FK506—including the reversible pontine demyelination seen in case 2 by NMR—resemble some of those ascribed to cyclosporine (7). In the cyclosporine reports, the neurotoxicity was associated casually with low cholesterol (8), hypomagnesemia (7), and aluminum overload (9). These latter findings are probably epiphenomena even if they are contributory to the pathogenesis.

A more fundamental explanation may be advanced for the neurotoxicity of these drugs.³ Although they are distinct, the binding sites of both cyclosporine and FK506 contain *cis-trans* peptidyl prolyl isomerase (10, 11). Inhibition of this enzyme could explain many metabolic effects of both drugs, including cholesterol regulation³ and reduction of magnesium (12). It is also doubtful that hypocholesterolemia has a direct casual role in the neurotoxicity (13). Although hypocholesterolemia is uniformly produced by FK506, the 2 examples of major neurologic complications herein reported were the only ones with a probable FK506 etiology seen in recipients of 180 livers, 55 kidneys, and 18 hearts, lungs, and heart-lungs treated primarily with this drug in the last 13 months. Seizures have occurred in

our liver transplant recipients with a lower frequency than in the past. Although we are making a systematic search to establish a specific etiology in each case, this has been difficult because of the multifactorial nature of this complication in liver recipients. Seizures have not been seen in the recipients of extrahepatic organs.

An important possibility is that there is a direct inhibitory effect of drugs like cyclosporine and FK506 on *cis-trans* peptidyl prolyl isomerase receptors in the central nervous system, as has been suggested elsewhere.³ Focal CNS targets made more susceptible by previous liver disease or any of the contributory factors mentioned earlier could be selectively affected by over-dosage. The first intravenous dose of 0.15 mg/kg FK506 used in our early experience has been reduced since to 0.075 mg/kg in order to reduce this possibility.

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ADJUVANT RADIOCHEMOTHERAPY FOLLOWING ORTHOTOPIC LIVER TRANSPLANTATION FOR BILE DUCT CANCER

Primary cancer of the bile ducts is an uncommon disease that accounts for 4500 new cancer patients annually in the United States (1). Although disease extension is generally locoregionally delimited at the time of surgery (2, 3), curative resection is possible in only 10–20% of cases (4). The pattern of locoregional recurrence in a significant percentage of patients (2, 5, 6) has led to evaluation of primary and adjuvant regional radiation therapy with suggestive but inconclusive results (6–8). Likewise, there are preliminary reports of combined-modality radiochemotherapy (9, 10). These studies are based on the low-but-definite response rates in patients with bile duct cancer treated with 5-fluorouracil (5-FU)* (11) and the potential for 5-FU radiosensitization (12).

Experience with orthotopic liver transplantation for bile duct cancer is limited, but the results are not impressive (13–18). The disease usually has recurred within the first year following surgery in patients who have survived the early postoperative period. Regional lymph nodes and the allograft are the most common sites of initial recurrence. In light of these disappointing results, three patients found to have bile duct cancer at the time of OLT for preoperative diagnoses of hepatocellular carcinoma (2) or recurrent bile duct adenoma (1) were treated with postoperative regional radiation and 5-FU radiosensitization. Our experience with these patients (described here) forms the basis of the protocol currently used at Baylor University Medical Center for patients undergoing OLT for unresectable nonmetastatic bile duct cancer.

The three patients had no evidence of gross extrahepatic, extranodal metastatic disease; had one or more high-risk factors for regional recurrence—e.g., hilar soft tissue invasion, perineural involvement, or metastatic disease to liver and/or regional lymph nodes; and had given informed consent.

Within five to nine weeks after OLT, radiation therapy was initiated to the targeted region of the porta hepatis and regional lymph nodes (including the celiac and pancreaticoduodenal nodal chains). Using 24 MeV x-rays via multiple-field techniques, 55.8 Gy was delivered in 31 fractions over 44 days. Concurrent 5-FU was administered by 96-hr intravenous infusion at a dose of 450 mg/m²/24 hr during weeks 1 and 4 of radiation. Patients received the usual postoperative immunosuppressive regimen, consisting of cyclosporine and methylprednisolone or prednisolone.

Case 1. A 39-year-old man developed diarrhea, nausea, vomiting, jaundice, and pruritus in April 1987. Serology indicated previous infection with hepatitis A, and a liver biopsy was nondiagnostic. Enterohepatic retrograde cholangiopancreatography (ERCP) was compatible with a diagnosis of sclerosing cholangitis. He was started on prednisone with initial clinical

and laboratory value improvement. Attempts to taper the steroids resulted in clinical deterioration, and the maintenance dose was increased to 60 mg daily in February 1988. Two months later, the patient developed fever, chills, and cough. A chest roentgenogram revealed a cavitary lesion. At bronchoscopy, a *Nocardia* infection was diagnosed, and he was started on trimethoprim-sulfamethoxazole with symptomatic improvement. Prednisone was tapered to 20 mg daily, and the patient was referred to this institution to be evaluated for possible liver transplantation. Magnetic resonance imaging revealed a large central liver defect, and a CT-guided biopsy taken on 6/13/88 was interpreted to be consistent with poorly differentiated carcinoma, most likely hepatocellular carcinoma. Physical examination showed jaundice with moderate muscle wasting. Neither the liver nor spleen was palpable. The serum alpha-fetoprotein level was 1.8 ng/ml (normal <18 ng/ml) and liver function studies showed total bilirubin 21 mg/dl, alkaline phosphatase 921, SGOT 207, SGPT 288, and LDH 291 U/L.

The patient was initially placed on our neoadjuvant chemotherapy-OLT protocol for hepatocellular carcinoma (19) and received a 28 mg/m²-cumulative dose of doxorubicin pre- and intraoperatively. After OLT on 6/24/88, histopathological examination revealed a cholangiocarcinoma (13×10.5×11.5 cm) centered at the confluence of the left and right hepatic ducts, scattered intraparenchymal lesions, focal invasion of connective tissue at the hilum, perineural invasion, and metastatic disease in one hilar lymph node. Radiation therapy and 5-FU were initiated six weeks postoperatively. Therapy was well tolerated without evidence of gastrointestinal or hematologic toxicity. He continues to do well 21 months posttransplantation without evidence of recurrent neoplasm by clinical, laboratory, or imaging criteria.

Case 2. This 35-year-old woman had right upper quadrant pain of three months' duration. Abdominal CT scan showed a mass (8 cm) in the central portion of the liver. On 7/1/88, tissue from a CT-directed liver biopsy was interpreted as consistent with hepatocellular carcinoma. MRI at Baylor University Medical Center confirmed the presence of a solitary mass (8×8×5 cm) at the juncture of the right and left portal veins. The patient had no history of liver disease, but family history disclosed that a maternal aunt had died at age 70 of a malignant liver tumor. Physical examination showed the liver edge palpable 4 cm below the right costal margin and extending into the epigastrium. The spleen was not palpable. Serum AFP was 3.1 ng/ml; HB_sAg and HB_eAb were negative; and liver function tests showed a normal bilirubin, minimally elevated transaminases, and alkaline phosphatase 230 U/L (normal <115 U/L).

The patient initially was entered on our neoadjuvant chemotherapy-OLT protocol, receiving 38 mg/m² cumulative pre- and perioperative doxorubicin (19). After OLT on 7/28/88, histopathological examination showed a cholangiocarcinoma

* Abbreviations: ERCP, enterohepatic retrograde cholangiopancreatography; 5-FU, 5 fluorouracil; MRM, modified radical mastectomy.