with intravenous trimethoprim-sulfamethoxazole (TMP-SMX) and improved quickly.

The symptoms of PCP worsen without appropriate therapy. As chest X-rays are often normal, as shown in our case 3, or show a faint ground-glass shadow, chest CT is very useful for detecting abnormalities at the early stage of PCP. This modality usually reveals bilateral diffuse ground-glass opacity. Diagnostic identification of \textit{P. carinii} is based on the microscopic detection of the organism in pulmonary materials. However, it is difficult to do such an invasive examination as bronchoscopy when the patient’s condition is worsening. Noninvasive diagnosis of \textit{P. carinii} infection using PCR of patient’s sputa is of great benefit.

For the prevention of PCP in patients with UC who are receiving immunosuppressive therapy, prophylactic treatment with TMP-SMX should be considered. Administration of prednisolone, at more than 16 mg/day over a 2-months period, or at 20 mg/day over a 4-weeks period, is suggested as the indication for preventive therapy. In the present case report, we have described three patients with UC who developed PCP during immunosuppressive therapy; one patient received pulsed steroid therapy, and two received AZA together with corticosteroids. Thus, we believe that prophylaxis has to be carried out in UC patients receiving immunosuppressive therapy with high doses of corticosteroid, as well as in those receiving combination therapy with corticosteroids and immunosuppressants such as AZA, considering the benefit of such prophylaxis and the high mortality of PCP.

Ryuta Takenaka, Hiroyuki Okada, Motowo Mizuno, Junichiro Nasu, Junichi Toshimori, Masashi Tatsukawa, Yasushi Shiratori
Department of Medicine and Medical Science, Okayama University Graduate School of Medicine and Dentistry, 2-5-1 Shikata-cho, Okayama 700-8558, Japan

Masaki Wato
Department of Internal Medicine, Mizushima Central Hospital, Kurashiki, Japan

Yasushi Tanimoto
Department of Hematology, Oncology and Respiratory Medicine, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan

References


Received: November 4, 2003 / Accepted: April 5, 2004
Reprint requests to: R. Takenaka
DOI 10.1007/s00535-004-1454-2

A pregnant patient with fulminant hepatic failure was found to carry a novel missense mutation in the argininosuccinate synthetase gene

Classical citrullinemia (CTLN1; OMIM no. 215700) caused by mutations of the argininosuccinate synthetase (ASS; EC6.3.4.5) gene on chromosome 9q34 differs from adult-onset type II citrullinemia (CTLN2; OMIM no. 603471), which is caused by mutations of citrin encoded by \textit{SLC25A13} on chromosome 7q21.3. Plasma citrulline/arginine levels enable the distinction of CTLN1 (2500 ± 1040/58 ± 31 nmol/ml) from CTLN2 with liver-specific ASS deficiency (521 ± 290/232 ± 167 nmol/ml). To date, 50 ASS mutations have been identified in CTLN1 patients, and differences among races have been noted.1 Most CTLN1 patients are neonatal- or infantile-onset, but some adult-
onset CTLN1 patients have also been found. Recently, we encountered a CTLN1 patient who developed fulminant hepatic failure during pregnancy, whose life could not be saved, despite the patient showing transient improvement following the initiation of treatment. Here, we report that the pregnant CTLN1 patient was a compound heterozygote with two different ASS mutations.

The patient was a 24-year-old Bolivian woman. From around 1993, she had occasionally experienced headache, dizziness during walking, and consciousness disturbance. In week 19 of pregnancy (October 1994), she reported nausea and weight loss (10 kg). After admission, she developed restlessness, abnormal behavior, and consciousness disturbance (Glasgow coma scale [GCS] score decreased to 4). She showed severe liver dysfunction, with hyperammonemia (143–624 µg/dl), and her prothrombin time (PT) was decreased, to 20%. At this point, fulminant hepatic failure was diagnosed, medical termination of the pregnancy was carried out, and plasmapheresis was performed. Her hepatic function improved, and consciousness level improved to a GCS score of 7. However, marked brain atrophy on magnetic resonance imaging (MRI) and significant slow waves on EEG were observed.

CTLN1 was diagnosed from her plasma aminogram: high citrulline (903–2740 nmol/ml) and low arginine (36–85 nmol/ml), and a protein-restricted diet and arginine therapy were initiated. Her consciousness level improved (GCS score, 12), but abnormal behavior was observed. Her condition subsequently remained stable for a while; however, her hepatic failure gradually worsened, and she died 8 months later, on May 30, 1995. On autopsy, large-droplet adipose degeneration occupied 90% of the liver (Fig. 1).

ASS activity in the autopsied liver specimen was undetectable, but levels of four other enzymes in the urea cycle were within the normal range, 50%–80% of control. In the present study, we performed reverse transcription-polymerase chain reaction (RT-PCR) and sequencing analysis of the entire coding region of the ASS mRNA. Two missense mutations, R86H and G390R, were identified and confirmed in the genomic DNA (Fig. 2). R86H is a novel mutation localized on exon 5 (G-to-A change at nucleotide 257; AciI loss). G390R is a common mutation in exon 15 (G-to-A at 1168 position; MspI loss). Genetic analysis revealed that the patient was a compound heterozygote with two different mutations in the ASS gene.

Gly-390 is conserved in the ASS protein from eight organisms, and G390R, which is found frequently in early-onset CTLN1 patients, is a severe mutation. However, Arg-86 is conserved only in mammals, and early-onset CTLN1 patients with an R86C mutation showed abnormal kinetics of the ASS enzyme. The R86H mutation, found in two adult-onset CTLN1 patients, our pregnant patient, and a 62-year-old patient, is associated with a milder phenotype than the R86C mutation.

Five pregnant or postpartum patients with CTLN1 were reported. Their initial symptoms were consciousness disturbance and aggressive behavior. These cases had been initially diagnosed as fulminant hepatic failure or acute fatty liver of pregnancy. For the diagnosis of patients with hyperammonemia and disturbance of consciousness in pregnancy, it is very important to determine plasma/serum amino acids.

Fig. 1A,B. Fine morphology of autopsied liver specimen from a 24-year-old pregnant citrullinemia (CTLN1) patient. The cytoplasm of the liver cells was filled with lipid droplets of various sizes (A) Lamellar bodies (arrows) and lipid droplets were present in the cytoplasm of the liver cells (B)