BRIEF REPORT

SYSTEMIC LUPUS ERYTHEMATOSUS AND ACUTE INTERMITTENT PORPHYRIA: COINCIDENCE OR ASSOCIATION?

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Since the first reported case in 1952 of systemic lupus erythematosus (SLE) associated with porphyria (1), there have been at least 25 other cases reported in the world literature (2). However, the diagnosis in some of these cases remains questionable because details about the type of porphyria seen in association with SLE were not always available. The purpose of this report is to describe the first case of acute intermittent porphyria (AIP) in association with SLE, in which the exact enzyme defect was measured by the erythrocyte uroporphyrinogen synthetase assay (URO-S) (3) to make a diagnosis of acute intermittent porphyria.

CASE REPORT

A 39-year-old white woman was transferred to Westchester County Medical Center with progressive stupor and hyponatremia.

She had been well until 2 years previously when she was admitted to another hospital with migratory polyarthralgias, facial butterfly rash, microscopic hematuria, albuminuria, hypergammaglobulinemia, false positive VDRL test results, and positive antinuclear antibody (ANA) test results. A diagnosis of systemic lupus erythematosus was made, but no treatment instituted.

Five months before admission to our medical center, she was readmitted to the first hospital, complaining of severe diffuse abdominal pains. Laboratory results included: a white blood cell (WBC) count of 6.8/mm^3, hematocrit of 33%, platelets 347,000/mm^3, erythrocyte sedimentation rate (ESR) 103 mm/hour, total serum protein 6.1 gm/dl with an albumin of 2.6 gm/dl and globulin of 3.4 gm/dl, and blood urea nitrogen (BUN) 27 mg/dl; creatinine, glucose, and electrolytes were normal. Urinalysis revealed a specific gravity of 1.010, ++ albumin, ++ blood, and 35–40 WBCs. Twenty-four hour urine showed 2.13 gm protein. The ANA was speckled with a titer of 1:640, C3 of 140 (normal 94–214), and antiDNA antibodies 19 units (normal <15). A diagnosis of active lupus with possible mesenteric vasculitis was made, and she was treated with 60 mg of prednisone; the dosage was slowly tapered to 10 mg daily after discharge.

She was readmitted to the same hospital 4 months later, when she complained of generalized and progressive abdominal pain radiating to the lower back and associated with malaise, nausea, and nonbloody diarrhea. There was no history of fever, chills, vomiting, hematemesis, or melena. Recurrent lupus mesenteric vasculitis was suspected, and the prednisone dose was increased to 60 mg a day. She was taking no other medications at this time. In the hospital the patient developed a grand mal seizure followed by a confused state, and phenytoin was started. Subse-

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quently, her blood pressure was noted to rise to 180/120. She was placed on propranolol, 160 mg/day, and her blood pressure decreased to normal.

Two days later, she became progressively stuporous. Physical examination revealed no focal neurologic deficit. Abdominal pain persisted, and prednisone was increased to 120 mg orally per day.

The following day, she developed a grand mal seizure and became progressively unresponsive. Physical examination at this time showed evidence of right sided weakness. Findings from lumbar puncture were normal. Electroencephalogram (EEG) revealed paroxysmal burst of slow wave activity with no clear focal or lateralizing features.

The next day, the seizure recurred. Electrolytes at this time were a serum sodium of 98 mEq/liter, chloride of 62 mEq/liter, and potassium 2.4 mEq/liter. Phenobarbital and appropriate fluid and electrolyte replacement were started, and she was transferred to Westchester County Medical Center for further evaluation and management.

Her medical history included tonsillectomy, cholecystectomy, appendectomy, and transient elevations of blood pressure. Menstrual periods were normal. She was gravida VI, para III with 3 spontaneous abortions. She had a history of drug allergy to sulfur and tetracycline. Family history was unremarkable for neurologic, endocrine, arthritic, or connective tissue disorders.

Physical examination findings included: temperature of 98.2°F, pulse 98/minute, respiration 20/minute, and blood pressure 136/98. She appeared well nourished and was in a semistuporous condition, responding only to noxious stimuli. Positive findings included diminished bowel sounds, a liver span of 14 cm, hypertonicity of her left arm, and bilaterally diminished deep tendon reflexes. The plantar reflexes were flexor.

Pertinent laboratory data included a WBC 26,800/mm^3 with 95% neutrophils, hematocrit 37%, platelet count 200,000/mm^3, ESR 18 mm/hour, sodium of 111 mEq/liter, potassium 2.7 mEq/liter, chloride 60 mEq/liter, BUN 30 mg/dl, creatinine 1 mg/dl, glucose 134 mg/dl, cholesterol 450 mg/dl, albumin 2.6 gm/dl, calcium 7.5 mg/dl, and magnesium 2.1 mEq/dl. Results of the antinuclear antibody test were strongly positive with a speckled pattern, C3 of 130 (normal 94–214), and antiDNA of 22 units/ml (normal <15). Urinalysis revealed a pH of 6, specific gravity 1.004, numerous red blood cells (RBC), and trace albumin. Occasional coarse granular casts and a moderate amount of bacteria were seen. Results of blood and urine cultures were negative. Spot urinary electrolytes showed sodium of 18 mEq/liter and potassium of 45 mEq/liter with a urine osmolality of 380 mOsm/kg and a serum osmolality of 250 mOsm/kg. Serum protein electrophoresis revealed hypoalbuminemia and hyperglobulinemia. Urine electrophoresis showed a small amount of albumin and globulins. Findings from radionuclide and computerized axial tomography scans of the head were negative. EEG again revealed diffuse slow wave activity with no clear focal or lateralizing features.

The patient's electrolyte imbalance was restored to normal within 48 hours with fluid restriction; there was only minor improvement in her mental status. Results of a modified Watson-Schwartz test for urinary porphobilinogen were highly positive and were later confirmed by a decreased level of uroporphyrinogen synthetase of 5 nmol URO formed/ml RBC/hour at 37°C [normal 21–35 by the method of Sassa et al (4)]. A diagnosis of acute intermittent porphyria was made, and phenytoin and phenobarbital were discontinued. The patient started to receive hypertonic glucose therapy (300 gm per day) in addition to 280 mg intravenous hydrocortisone daily, but no improvement was noted.

High-dose intravenous propranolol therapy was subsequently started. A total dose of 386 mg propranolol was given during an 18-hour period, but she did not respond. On the fifty-eighth hospital day, she developed septicemia with *Enterobacter aeroginosa*. Despite aggressive treatment with appropriate antibiotics, the patient died. No postmortem examination was obtained.

DISCUSSION

Of the 25 reported cases (2) of SLE associated with porphyria, 18 cases of SLE have occurred in association with porphyria cutanea tarda, 6 with acute intermittent porphyria, and 1 with porphyria variegata. This breakdown is questionable since the type of porphyrin present in the urine and/or feces was not always reported and no enzyme assays were available. The case reported here is the first of acute intermittent porphyria in association with systemic lupus erythematosus in which the erythrocyte uroporphyrinogen synthetase assay was used to demonstrate the enzyme deficiency (3) and make a specific diagnosis of AIP.

Until recently, the diagnosis of AIP was based on clinical findings and the increased urinary porphyrin precursors; δ-aminolevulinic acid (ALA) and porphobilinogen (PBG). Although the urine quantitative

measurements using chromatographic methods and the qualitative Watson-Schwartz test for porphobilinogen are useful in acute cases of AIP, they have not been found to be reliable in latent cases (5). It has also been shown that some patients without symptoms may excrete more porphobilinogen than others with an active disease process (6).

In addition, the Watson-Schwartz test may yield falsely positive results secondary to substances such as pyridium, beet pigment, melanogen, or urobilinogen (6), which decreases its reliability.

The erythrocyte URO-S assay that was used in our case has proved to be a highly reliable method of diagnosing AIP. A positive result is indicated by a URO-S level less than 50% of normal (6).

SLE and AIP have a number of common features that make the differential diagnosis difficult, including fever, rashes, photosensitivity, mucous membrane lesions, gastrointestinal symptoms, changes in electrocardiographic findings, central nervous system changes (psychosis, convulsions, headache, neuropathy, paralysis), and syndrome of inappropriate antidiuretic hormone secretion. When the two diseases occur in the same patient, one of the diagnoses may easily be missed.

The neuropsychiatric symptoms common to both conditions are present in AIP, porphyria variegata, and hereditary coproporphyria, but are usually absent in porphyria cutanea tarda, erythropoietic protoporphyria, and secondary porphyrinurias. These manifestations include psychiatric disturbances such as organic mental syndromes, depression, assorted neuroses, and occasional schizophrenia (7), as well as organic disorders as manifested by motor paralysis (8), sensory loss, or autonomic neuropathy (9). Autonomic neuropathy has been implicated in the pathogenesis of abdominal pain, tachycardia, labile blood pressure, and excessive diaphoresis (9). The increased urinary excretion of ALA and PBG in acute intermittent porphyria does not correlate with the presence or degree of central nervous system (CNS) involvement (7). Many patients with increased levels of ALA and PBG in the urine have none of the neuropsychiatric manifestations of porphyria.

The central nervous system manifestations of SLE are similarly varied, occurring in approximately two-thirds of patients with this disease (10,11). The most common presentation is psychosis (11); other manifestations include seizures, peripheral and cranial nerve involvement, hemiplegia, chorea, arachnoiditis, meningitis, and headaches (10,11).

The pathogenesis of central nervous system lupus remains vague and unclear in most instances. Johnson and Richardson (12) demonstrated vasculitis, microinfarcts, and demyelination of the central nervous system and peripheral nerves. Atkins et al (13) found globulin deposition characteristic of immune complexes in the choroid plexus of 2 patients dying of CNS lupus. Lampert et al (14) demonstrated in NZB/NZW mice that the immune deposits are secondary to DNA-antiDNA complexes. More recently, Bluestein (15) showed the presence of neurocytotoxic antibodies in sera of patients with SLE.

The patient reported here came to us with predominately abdominal and central nervous system symptoms. It was not possible to ascertain which of the disease entities was responsible for the symptoms.

The occurrence of SLE and porphyria in the same patient has repeatedly raised the question of association or coincidence. The intriguing question of whether SLE and porphyria have a common pathogenetic mechanism remains unanswered. Both diseases are precipitated by factors such as fatigue, sun exposure, and drugs (16). At least in the patient presented here, it is possible that the porphyria was precipitated by the use of phenytoin, which was used in the control of the seizure. It is also possible that seizure was an early manifestation of porphyria.

Numerous theories have been proposed to explain the association between SLE and porphyria. These include: 1) a chance association of the two disorders, 2) a shared genetic defect, 3) an autoimmune disorder resulting from SLE and leading to porphyria, 4) an acquired metabolic defect in lupus leading to porphyria, and 5) SLE exposing a genetic defect that precipitates the appearance of porphyria (17).

Supportive evidence for this association has come from direct immunofluorescence studies on epidermal basement membrane and dermal blood vessels of both SLE and porphyria cutanea tarda patients. Skin biopsy specimens of patients with SLE and of patients with porphyria cutanea tarda showed similar patterns of deposition of immunoglobulin, usually IgG and sometimes complement (18,19).

Indirect evidence for the association comes from reports of several other autoimmune disorders that were linked with various types of porphyria. Porphyria cutanea tarda has been reported in association with scleroderma (20,21), thymoma (22), and autoimmune hemolytic anemia (23–25).

Considerable advances have been made in the treatment of SLE with the introduction of steroids and immunosuppressive agents. However, the benefit of

this mode of therapy in CNS lupus is controversial (11). Similarly, there have been newer methods of treatment introduced in the management of porphyria, including hypertonic glucose infusions (26), high-dose intravenous propranolol (27), and heme infusions (28).

Our patient underwent hypertonic glucose therapy without success. In view of the benefits from high-dose propranolol therapy reported by Douer and his group (27) in a patient with AIP, we elected to treat our patient with this modality. A total dose of 286 mg of propranolol was given intravenously over an 18-hour period and then continued at 200 mg/day for 2 days. Even though these doses exceeded Douer's recommendations, our patient did not respond.

This case illustrates the coexistence of these two diseases and the difficulties in distinguishing which disease is responsible for the symptoms in an individual patient.

The question of whether acute intermittent porphyria and systemic lupus erythematosus are somehow linked remains intriguing but unanswered.

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