

PORPHYRIA CUTANEA TARDA ASSOCIATED WITH LYMPHOMA

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Abstract. Three patients with porphyria cutanea tarda and lymphoma were seen at the Mayo Clinic. In one patient, the signs and symptoms of porphyria cutanea tarda and lymphoma occurred simultaneously, whereas in the other two, the porphyria was seen before the lymphoma occurred, three years before in one and one and a half years before in the other. Involvement of liver or marrow was not related to the development of porphyria cutanea tarda in any of the 3 patients. The porphyria cutanea tarda was not eased by radiotherapy or chemotherapy of the lymphoma, although it was probably less symptomatic after the patients were treated. While a relationship between porphyria cutanea tarda and lymphoma is speculative, confirmation will require a closer scrutiny of patients with these two diseases.

Key words: Systemic disorders; Lymphocytic lymphoma

Porphyria cutanea tarda has been noted in association with several systemic disorders including systemic lupus erythematosus (2), diabetes mellitus (7), erythrocytosis (9), and hepatoma (8). Harber (3) noted isolated cases in association with Hodgkin's disease, carcinomatosis, and reticuloendotheliosis. One patient with porphyria and lymphosarcoma also has been described (6). An association between these diseases and porphyria cutanea tarda has been determined only for hepatoma, erythrocytosis, diabetes mellitus, and lupus erythematosus.

Recently, we saw a patient with undifferentiated lymphocytic lymphoma in addition to porphyria cutanea tarda. We questioned the significance of this occurrence. Therefore, a computerized cross-check was done of diagnoses of various types of lymphoma and porphyria cutanea tarda in patients seen at the Mayo Clinic between 1960 and 1977, and two additional patients were found. We will describe these three patients and review the data on other similar patients reported in the literature. In particular, we wanted to evaluate the effect of treatment of the lymphoma on the porphyria cutanea tarda.

REPORT OF CASES

Case 1

A 48-year-old woman was well until 1972, when she noted an increase in facial hair growth. Up to this time, the patient had been taking contraceptive pills for many years and was a heavy drinker of alcohol. In 1974, bullae began to develop on the dorsa of her hands. Liver function tests showed only a mildly increased level of serum lactic dehydrogenase. The hemoglobin level, erythrocyte count, and serum iron concentration were all in the high-normal range. The urinary levels of porphyrins were elevated. The patient was treated with phlebotomy of 4 units of blood and sunscreen lotions and improved. There was no family history of porphyria and no history of abdominal pains or psychotic episodes.

In 1975, the patient began to have dysfunctional uterine bleeding. Endometriosis was diagnosed clinically and histopathologically, and she underwent total abdominal hysterectomy. Liver biopsy showed only fatty, degenerative changes. In August 1975, the patient began to drink alcohol again. Her symptoms of porphyria cutanea tarda flared, and urinary uroporphyrin excretion measured at her local hospital was 2 350 $\mu\text{g}/24 \text{ h}$ (normal 0 to 26). She improved with alcoholic abstinence until May 1976, when she again noted recurrent, sun-related bullae of the hands. More hypertrichosis of the face was apparent. She noted tiredness and lethargy. Serum lactic dehydrogenase concentration at that time was 1 095 U/l (normal 100 to 225). She did not improve despite several more phlebotomies and abstinence from alcoholic drinks.

In June 1976, she started taking methyl dopa and a drug containing triamterene and hydrochlorothiazide for hypertension. In October 1976, the patient was seen at the Mayo Clinic and was noted to have increased facial hair, facial suffusion, and multiple bullae and scars on the dorsa of her hands. She had recently lost 13.6 kg and complained of indigestion and food intolerance. The patient also complained of recent hematuria with clots. The urine showed large amounts of free hemoglobin and proteinuria (1+ to 2+). An excretory urogram showed a mass in the upper pole of the right kidney. Cystoscopy showed no abnormality. Cholangiograms showed gallstones.

In November 1976, the patient underwent a right nephrectomy and partial ureterectomy, with removal of retroperitoneal lymph nodes. Pathologic examination showed malignant lymphoma of the diffuse undifferentiated lymphocytic type, diffusely infiltrating the kidney, involving vessels, and penetrating the renal capsule

Table 1. *Porphyria cutanea tarda associated with lymphoma*

	Case 1	Case 2	Case 3	Rayhanzadeh's case (6)
Age at diagnosis of porphyria (year)	48	56	65	63
Age at diagnosis of lymphoma (year)	52	56	67	63
Type of lymphoma	Undifferentiated	Hodgkin's disease (lymphocyte predominance)	Lymphocytic lymphoma of skin: (?) mycosis fungoides	Lymphosarcoma
Site of lymphoma	Liver, kidney, lymph nodes, central nervous system	Lymph nodes (stage III B)	Skin	Bone marrow
Effect of lymphoma treatment on porphyria	Improved	None or better	None	None or better
Predisposing factors for porphyria	Alcohol, contraceptive pills	Alcohol	Alcohol	None
Survival after diagnosis of lymphoma	6 months	4 years	1 month	...
Other malignancy	None	Malignant fibrous histiocytoma	None	None
Hemoglobin (g/dl)	14.2	15.1	15.8	...
Marrow iron stains	Normal	Normal	Normal	...

and perinephric fat. The lymph nodes showed early malignant lymphomatous involvement. Three liver biopsy specimens showed Kupffer cell hyperplasia only. The urinary level of uroporphyrins was markedly elevated to 1449 $\mu\text{g}/24\text{ h}$ (normal 10 to 60). Coproporphyrin excretion in the stool also had increased to 1074 $\mu\text{g}/24\text{ h}$ (normal <200). Bone marrow examination and biopsy showed moderate fibrosis and distorted architecture; there were two foci of mature lymphoid elements highlighted with eosinophils. This was interpreted as being suggestive of involvement of the marrow with lymphoma but not diagnostic of it, and diffuse pleomorphic lymphoma, stage II_FA, was diagnosed.

The patient began a 14-day cyclic regimen of prednisone, cyclophosphamide, vincristine, and procarbazine from Dec. 7 to Dec. 21, 1976. On Dec. 23, 1976, the patient returned with a 2-day history of severe right-sided headaches and a 1-day history of incoherency. Spinal fluid examination revealed no abnormality. The patient was given 15 mg of methotrexate intrathecally, but that night she had two grand mal seizures. The following day she could not be aroused, her left pupil was larger than her right, and her eyes deviated to the right. An electroencephalogram was suggestive of a left hemispherical posterior lesion.

The patient was given two treatments of 250 rads to the head 24 hours apart and in 24 hours was alert and feeling much better. She was given dexamethasone, 2 mg every 6 hours orally, and during the next few days, radiation therapy was continued to a total of 3250 rads, and the patient improved. The patient was also given diphenylhydantoin, cephalothin, and gentamicin. On Dec. 28, 1976, the patient had another spinal tap (normal), and another 15 mg of methotrexate was given intrathecally.

On Dec. 21, 1976, the patient had been noted to have one bulla on her right hand—the first bulla to be seen in more than 3 months. However, other signs and symptoms of porphyria cutanea tarda were not found. The 24-hour urinary excretion of porphyrins showed a pronounced decrease—to 455 $\mu\text{g}/24\text{ h}$ for uroporphyrins and to 129 $\mu\text{g}/24\text{ h}$ for coproporphyrins (normal up to 211). The porphobilinogen and Δ -aminolevulinic acid levels were normal, 0.5 U/24 h (normal ≤ 2 U), and 2.3 mg/24 h (normal 1.5 to 7.5 mg), respectively.

The patient was dismissed from the hospital on Jan. 16, 1977, and received three more courses of prednisone-cyclophosphamide-vincristine-procarbazine at monthly intervals. The symptoms of porphyria cutanea tarda did not seem to change during this time, although they may have improved.

In mid-March, the patient noted anorexia and decreased strength, after which lethargy increased, progressing to obtundency. Spinal tap, EMI scan, and many blood cultures were all negative. Her temperature was elevated to 102°F (38.9°C). Her hemoglobin level decreased to 7.8 g/dl, with a smear suggestive of hemolysis, and she was given 2 units of whole blood.

The patient then developed what was considered to be subacute cholecystitis and underwent cholecystectomy on Apr. 1, 1977; the gallbladder removed at surgery contained 10 gallstones 0.5 to 1 cm in diameter. She was given 20 million units of penicillin G intravenously for 24 hours and 60 mg of gentamicin every 12 hours. Eight days post-operatively, she had increasing creatinine levels, which reached 7.2 on Apr. 21, 1977. The patient died the next day.

Autopsy revealed diffuse malignant lymphomatous involvement in the liver and in the remaining kidney. The

brain was not evaluated at autopsy. Cause of death was renal failure.

Case 2

A 56-year-old man was well until January 1968, when he began to have headaches and noted tender subcutaneous nodules on the upper part of his back near the midline. During the next few months, he also had easy fatigability and loss of appetite and he lost 6.4 kg.

In November 1968, the patient was seen again, with lymphadenopathy in the right anterior cervical and nuchal areas. He had a 4- by 8-mm ulcer in his right axilla and an 8- by 15-mm ulcer on the lower part of his left leg: the ulcers had begun as pustular lesions 3 weeks earlier. His face was suggestive of porphyria cutanea tarda with suffusion and hypertrichosis. No blisters or crusts were present. He had a 15-20 year history of moderately heavy intake of alcohol.

A cervical lymph node biopsy showed Hodgkin's disease of the lymphocyte predominant type. The liver and spleen were not palpable. Roentgenograms, lymphangiograms, and biopsy specimens revealed involved nodes in the para-aortic, right paratracheal, right supraclavicular, and right iliac regions. The patient was considered to have stage III B disease and was treated with radiation therapy, receiving 300 rads per treatment for 32 treatments through ports covering the abdomen, inguinal, paratracheal, and scalene regions.

The urinary uroporphyrin level was 1 140 $\mu\text{g}/24$ h, the porphobilinogen level was 0, and the coproporphyrin level was 2 330 $\mu\text{g}/24$ h in November 1968. Porphyria cutanea tarda and alcoholism were diagnosed. The patient was told to abstain from alcohol and given a high protein, high calorie diet.

The patient had no recurrence of the lymphoma, but in September 1972, he became acutely ill and died. Autopsy revealed widespread metastatic lesions of malignant fibrous histiocytoma in the stomach (which was perforated) and in the liver, lungs, lymph nodes, brain, kidneys, adrenal, and left ear. There was no evidence of residual Hodgkin's lymphoma. Clinically, there had been little change in the porphyria.

Case 3

A 68-year-old man was first seen in May 1970 because of a 3-year history of bullae and easy bruisability of the dorsal aspects of his hands and fingers, as well as increased fragility of his skin. The patient also had a one and a half year history of recurrent ulcerations on the right thorax, back, and scalp. A diagnosis of mycosis fungoides had been made elsewhere, and radiation therapy was given to these areas in 1968. The patient had a long history of drinking, usually 2 glasses of Scotch whisky nightly.

In 1970, he was first seen at the Mayo Clinic, where physical examination revealed bronze skin, "liver palms", facial suffusion, asteatosis, marked actinic changes in sun-exposed areas, and three bullae on the dorsa of the hands. Also noted were multiple abrasions and ruptured bullae. Lymphadenopathy was not present, and the liver and spleen were not palpable.

In addition, the patient had several erythematous and violaceous infiltrated plaques up to 4 cm in diameter,

some of which were superficially ulcerated on his thorax and right flank. He also had scarring and alopecia of the scalp, face, and dorsum of the hands. Biopsy of a right flank lesion showed a dense dermal and subcutaneous infiltrate of large atypical lymphocytes which was considered to be more consistent with lymphosarcoma than with mycosis fungoides. Parapsoriasisiform or eczematous plaques were not present.

The urinary level of uroporphyrin was 3 650 $\mu\text{g}/24$ h and that of coproporphyrin 8 400 $\mu\text{g}/24$ h. Stools showed coproporphyrins 2 210 $\mu\text{g}/24$ h, protoporphyrins 2 440 $\mu\text{g}/24$ h, and uroporphyrins 1 030 $\mu\text{g}/24$ h. Sulfobromophthalein retention was 9% at 45 min. A pedal lymphangiogram and bone marrow biopsy and examination showed no abnormalities.

The patient was told to refrain from alcohol and given 15 mg of prednisone daily. He also had topical applications of nitrogen mustard in a dilution of 20 mg/dl.

A few months later, in September 1970, he became acutely ill with an apparent urinary tract infection and died; autopsy was not performed.

COMMENT

Data on our 3 patients and the patient of Rayhanzadeh et al. (6) are summarized in Table I. We could find only one other mention of an association between porphyria cutanea tarda and lymphoma. The clinical and laboratory data fit best with a diagnosis of porphyria cutanea tarda. There were no other cases of porphyria in the families of these patients, as is generally true of porphyria cutanea tarda (5). Recent data have shown a genetic defect in patients with porphyria cutanea tarda, resulting in decreased levels of uroporphyrin decarboxylase (4). This has been found to be transmitted as an autosomal dominant trait in at least several cases (1). However, the clinical expression of this defect is variable. Some patients who have a smaller decrease in the amount of the enzyme do not have any clinical manifestations of porphyria cutanea tarda. These uroporphyrin decarboxylase studies were not done in any of our patients or any of their relatives.

Harber (3) reported a patient with Hodgkin's disease and porphyria cutanea tarda but gave no details. In all 4 patients, porphyria cutanea tarda was diagnosed within 4 years of the diagnosis of the lymphoma. All 4 had typical cutaneous findings of porphyria cutanea tarda, and 3 of the 4 had blisters on the hands. Photosensitivity was clinically evident in one of the four (case 2). One patient (case 1) had the longest interval (4 years) of porphyria cutanea tarda symptoms before lymphoma was diagnosed, while in one (case 3) the porphyria

cutanea tarda had been present for approximately one and a half years. In each of the other 2 patients, the diagnoses were made almost simultaneously. The porphyria cutanea tarda was not severe or disabling in any patient. Special bone marrow stains for iron did not reveal iron overload in any of our patients, although one (case 1) had had phlebotomy of 4 units initially. In no patient was the porphyria cutanea tarda considered to be caused by lymphomatous involvement of the liver or bone marrow. Consideration was given to the possibility that the abdominal crisis in one (case 1) was related to the porphyria disorder, especially since autopsy had revealed extensive lymphomatous infiltration of the liver. However, previous tests for porphobilinogen had been negative, and signs and symptoms of cholecystitis, as well as gallstones, were present. Also, lymphomatous involvement of the remaining kidney was extensive, readily explaining the renal failure. Treatment of the lymphoma did not seem to aggravate the porphyria cutanea tarda in any of the patients. Radiation therapy, prednisone, topically applied nitrogen mustard, and polychemotherapy were all used, and none exacerbated the porphyria cutanea tarda. In fact, the signs and symptoms of porphyria cutanea tarda improved in each patient after treatment of the lymphoma. Urinary porphyrin levels were noted to be greatly decreased after treatment in one patient.

The 4 patients had differing kinds of lymphoma. What the relationship might be between porphyria cutanea tarda and lymphoma is speculative. Nevertheless, the possibility of such an association requires a more careful evaluation of patients with either of these conditions.

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Received June 3, 1978

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