# Thiamine Deficiency in Hematologic Malignant Tumors

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**The case is reported of a patient with acute myeloid leukemia with severe right-sided congestive heart failure that responded to treatment with thiamine. Leukocytes cells contain relatively high concentrations of thiamine-dependent enzymes compared with erythrocytes. Because no other cause could be found, it was postulated that consumption of thiamine by blast cells was responsible for the deficiency. After studying this patient, the thiamine pyrophosphate (TPP) effect was measured in five other consecutive patients with fast-growing hematologic malignant tumors. In two patients, the TPP effect was elevated slightly, but another patient had a definite thiamine deficiency with severe cardiac failure. It is suggested that the clinician be alert for this underdiagnosed potentially fatal but easily treatable deficiency in nonalcoholic patients with fast-growing hematologic cancers.**
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Thiamine is synthesized by many plants and microorganisms but, with a few exceptions, not by mammals. In the normal human, approximately 30 mg is stored in the body, of which 80% is thiamine diphosphate or pyrophosphate (TPP). Required for various reactions that cleave carbon–carbon bonds, TPP is a coenzyme for pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and transketolase. It also plays a direct role in the excitability of neurons.[1]

The recommended daily intake of thiamine is 1 mg. Thiamine deficiency develops in people whose diets contain less than 0.2 mg/day. After several months of such a diet, cardiovascular and neurologic changes occur.[2–4] Clinical thiamine deficiency is rare in the West, except in conditions that interfere with ingestion or absorption of food for long periods. Alcoholism is the main example of such a condition, but other chronic illnesses can also produce thiamine deficiency.[5]

Thiamine is absorbed by active and passive mechanisms. The active mechanism is blocked by alcohol interference with sodium–potassium adenosine triphosphatase; alcoholism and extensive disease or resection of the small intestine seem to be the only causes of thiamine malabsorption.[6] We report another possible cause for thiamine deficiency, namely consumption by tumor cells, in patients with fast-growing hematologic tumors.

## Case Reports

### *Case 1*

A 62-year-old man with no medical history was admitted to our hospital with complaints of fatigue and exertional dyspnea for the past 2 weeks. His temperature at home was 38°C. He was not dieting or abusing alcohol, and there was no vomiting. The patient was pale, and results of the physical examination showed a blood pressure of 160/75 mmHg, pulse rate 88 beats/min, temperature of 38.5°C, weight of 105 kg, and height of 1.85 m. There were no neurologic abnormalities. The jugular veins were extended, and the patient had cardiomegaly, a gallop rhythm, and pleural effusions. The liver was palpable 7 cm under the right costal margin. There was pitting edema of the legs.

Results of electrocardiography showed sinus rhythm with atrial enlargement and no signs of recent or old myocardial infarction. Results of chest radiography showed cardiomegaly, pulmonary congestion, and predominantly left-sided pleural effusion.

Results of laboratory examination showed a hemoglobin level of 5.5 mmol/l, leukocyte count of $69.1 \times 10^9$/l (largely blast cells), platelet count of $22 \times 10^9$/l, uric acid level of 0.44 mmol/l (normal, less than 0.45 mmol/l), and lactate dehydrogenase level of 288 units/l (normal, less than 120 U/l). His bone marrow was infiltrated diffusely with myelomonoblasts. The diagnosis of acute myelomonocytic leukemia (AML-M4) was made with predominantly right-sided congestive heart failure. For his leukemia, the patient was treated with mitoxantrone and cytarabine (Fig. 1). Despite a salt-restricted diet and high doses of furosemide, his congestive

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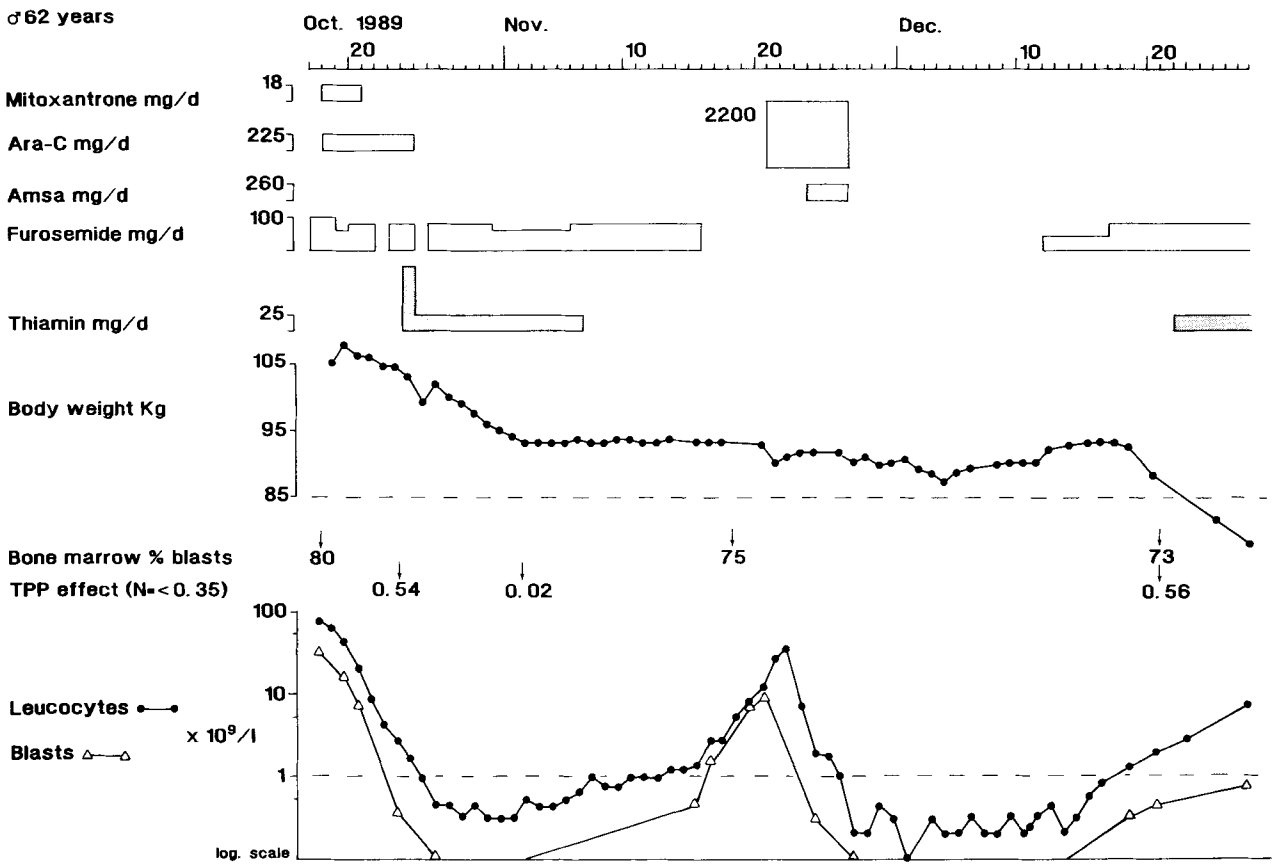


Figure 1. Clinical and laboratory parameters in Patient 1.

heart failure did not improve, and his weight rose to 108 kg. Therefore, although there was no history of alcohol abuse, we suspected thiamine deficiency.

His thiamine status was assessed by the whole-blood transketolase activity with and without TPP; the degree of activation produced by adding TPP was calculated as a percentage. A normal result in our laboratory is a transketolase activation less than 35%. Those with thiamine deficiency have a higher activation. In this patient, the TPP effect appeared to be 0.54; therefore, 100 mg of thiamine was given, followed by 25 mg per day orally. Within 10 days, the edema disappeared and the weight of the patient decreased to 93 kg (Fig. 1). The TPP effect became normal (0.02). After 2 weeks, thiamine supplementation was stopped. Bone marrow aplasia of 2-weeks duration developed. The patient had a good appetite and ate all his meals, including ingesting 400 ml of Fortimel (Nutricia Nederland BV, Zoetermeer, The Netherlands) per day, a nutritional supplement containing 0.17 mg/100 ml of thiamine. There was no vomiting. After 3 weeks, blast cells reappeared in the peripheral blood, and the patient was treated with cytarabine and amsacrine (Fig. 1).

Three weeks after starting this therapy, the patient again had edema and gained weight. He was treated with furosemide. After the TPP effect appeared to be 0.56, thiamine 25 mg per day was restarted. At the same time, the number of blasts in his peripheral blood rose, and his hypercellular bone marrow showed 73% myelomonocytic blasts. Therefore, it was concluded that the leukemia was refractory. No further remission–induction treatment was given, and the patient died shortly after of infection.

After studying this patient, we measured the TPP effect in five other consecutive patients with high-grade hematologic tumors (Table 1). Two patients had a normal TPP effect in two, it was elevated slightly; and in one (Patient 2), there was a definite thiamine deficiency.

To exclude consumption of thiamine *in vitro*, we later measured the TPP effect in eight patients with leukocytosis (greater than or equal to $10 \times 10^9$/l) in blood anticoagulated with heparin and fluoride. There were no significant differences using these two methods (heparin [mean TPP effect, 0.16; standard deviation, 0.11] and fluoride [mean TPP effect, 0.20; standard deviation, 0.09]).

## *Case 2*

A 29-year-old woman was admitted to another hospital because of abdominal pain for the past 2 weeks. She had no medical history, was not dieting or abusing alcohol, and was not vomiting. At laparotomy, a large Burkitt's lymphoma was found. Supplementary investigations showed no other locations. Twelve days after surgery and 2 days before admission to our hospital, she received cytostatic treatment consisting of cyclophosphamide 500 mg intravenously, vincristine 1.7 mg

**Table 1. Thiamine Pyrophosphate Effect and Characteristics in Six Consecutive Patients with Fast-Growing Hematologic Malignancies**

| Patient no. | Sex/age (yr) | Diagnosis | TPP effect (normal < 0.35) | Leukocytes in peripheral blood ($\times 10^9$/l) | Clinical manifestations |
|---|---|---|---|---|---|
| 1 | M/62 | AML-M4 | 0.54/0.56 | 69.1 | Yes |
| 2 | F/29 | Burkitt's lymphoma | 0.74 | 15.9 | Yes |
| 3 | F/48 | ALL | 0.39 | 21.7 | No |
| 4 | F/43 | Burkitt's lymphoma | 0.39 | 32.0 | No |
| 5 | F/27 | AML-M2 | 0.19 | 2.1 | No |
| 6 | F/27 | AML-M3 | 0.16 | 2.7 | No |

TPP: thiamine pyrophosphate; AML: acute myeloid leukemia; M4: acute myelomonocytic leukemia; ALL: acute lymphocytic leukemia; M2: acute myeloblastic leukemia; M3: acute promyelocytic leukemia.

intravenously, and prednisolone 100 mg orally for 5 days (COP). During the next few days, the patient became oliguric, and serum creatinine level rose to 298 μmol/l, phosphate to 5.54 mmol/l (normal, 0.7 to 1.45 mmol/l), and potassium to 6.1 mmol/l (normal, 3.5 to 4.5 mmol/l). The patient was transferred to our hospital with a diagnosis of acute tumor lysis syndrome.

Apart from ascites, results of the physical examination conducted at hospital admission showed no abnormalities. The patient received hemodialysis seven times; after this, diuresis and blood values improved. We decided to give her another course of COP treatment, identical to the first one. Although no signs of heart disease were initially present, 2 days after the start of chemotherapy, the patient had massive congestive heart failure on both sides. Myocardial infarction was excluded biochemically, and results of echocardiography showed dilatation and diminished contractility of all compartments of the heart. The patient was treated with nitroprusside, dopamine, and furosemide. After the TPP effect was found to be 0.74 (normal, less than 0.35), thiamine 50 mg daily was added. With this treatment, her clinical situation improved dramatically. After a few days, the patient returned to the hospital that referred her for additional treatment of Burkitt's lymphoma.

## Discussion

In two of six consecutive patients with a fast-growing hematologic tumor, a thiamine deficiency was documented. Both had severe cardiovascular symptoms that rapidly responded to thiamine supplementation. No neurologic complications, such as nystagmus, abducens paralysis, ataxia, stupor, or coma, were observed. Two other patients had a borderline increase in the TPP effect without clinical symptoms.

All patients were ill for a short period, and none had a history of alcohol abuse, vomiting, or malnutrition. It takes weeks to months of poor nutrition before a thiamine deficiency develops, and it is relatively rare in the West except for alcohol abusers.[7] Malabsorption from mucosa atrophy caused by cytostatic treatment could not be the cause of the thiamine deficiency because the TPP effect was measured before or shortly after starting treatment. An *"in vitro"* cause of the elevated TPP effect related to consumption by cells *in vitro* was excluded because there were no significant differences between the TPP effects determined in heparinized and fluoridated blood. Fluorides are cellular poisons that inhibit metabolism by blocking a number of enzymatic reactions.

In our four patients, we could not find a cause for the thiamine deficiency except the possible relationship with the acute leukemia or Burkitt's lymphoma. Patient 1 had a recurrence of the thiamine deficiency with clinical symptoms at the same time that his leukemia relapsed. In the intervening period, his food intake had been normal.

Leukocytes contain relatively high concentrations of thiamine-dependent enzymes.[8,9] In humans, it was found that the transketolase activity in leukocytes was 93-fold higher than in erythrocytes.[9] We hypothesize that these fast-growing hematologic cancers consume thiamine, leading to a deficiency. We have not found other clinical reports concerning thiamine deficiency and hematologic tumors, but it has been documented in experimental tumors. In mice with Ehrlich ascites carcinoma, a fast-growing experimental tumor, such an effect was documented.[10] Tumor growth was accompanied by thiamine deficiency, manifested by an increase in $^{14}$C-thiamine incorporation into the host tissues. Increased values for the turnover coefficients, reduction of thiamine-dependent enzyme activities, elevation of the TPP effect, and a decrease in urinary excretion of the radioactive products also provided evidence for the thiamine deficiency.

Our two case reports show that we must be alert for life-threatening complications of thiamine deficiency in patients with highly malignant hematologic disorders who do not abuse alcohol. Another important point to consider is whether to withhold effective cytostatic drugs, like the anthracyclines, from patients with car-

diovascular symptoms if thiamine deficiency is the cause of these symptoms that are easily reversible by thiamine supplementation.

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