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Case Report

Thiamin Therapy of Lymphoma

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Abstract

A patient with typical NK/T lymphoma of nasal type was treated with parenteral thiamin 100 mg twice a day plus 1 ampule of vitamin B complex for 10 days. Nasal signs and fever greatly improved. Then thiamin increased as 200 mg twice daily for next 4 months. Nasal signs including fever disappeared, daily farming and driving restored, and lab test greatly improved. However, the patient erroneously believed to be well cured and discontinued parenteral vitamins for 3 months. Totally, the patient was getting free from signs and symptoms for 7 months. Nasal signs then returned and chemo- and radiotherapy were held, January 5-15, 2013. Within 2 months, oral palate entirely perforated. He became extremely powerless and confined to bed until his death, June 29, 2013.

Keywords: *Baker's Cyst; Lipoma; Lymphoma; Osteosarcoma; Submandibular Gland Cyst; Thiamin*

Introduction

Thiamin therapy was based on: 1. Clinical observation in a population with inadequate food and terribly hard labor, 1958-1962. In the year 1959, intra-mass injection of thiamin was found dramatically effective in replacing surgery for eradicating lipoma, submandibular gland cyst and Baker cysts. And subcutaneous infusion of thiamin reduced osteosarcoma drastically. 2. Enlargement of lymph nodes in armpit and groin were as common as 40% in this population. 3. Recently, some researchers confirmed that high dose of thiamin reduced proliferation of cancer cells. Therefore, parenteral thiamin was tried. It proved that, thiamin was life-saving while current traditional radio- and chemotherapy, lethal. More cases are needed to reject radio- and chemotherapy.

Interpretation of Abbreviations

1. AP-1 and NF- κB stand activator protein-1 and nuclear factor κB. K is a Greek letter. They are activating transcription factors, which can cause transcription of genes involved in cell growth if stimulated by reactive oxygen species (ROS).
2. CD stands for Cluster of Differentiation, a big complicated word which means antigens on the cell surface marked with a number, such as CD20, CD19, CD30 etc.
3. Ki-67 is the name for a protein found in some cells. Its high level generally indicates a more aggressively growing clone of cells.
4. NK/T means Natural Kills Cells and T-cells. This is a kind of lymphoma of NK and T-cell commonly involving Asians.
5. Panc-1 is a pancreatic cancer cell line and SK-N-BE is a neuroblastoma cell line.

Case Report

Mr. Li, S, a farmer of 40 in Tianjin west of China became suffering from frequent smell breath, smell liquid or solid discharge and nasal bleeding or fever on February 2012. Computed tomography scan after 3 months in Tianjin People's Hospital revealed tissues covering all sinuses and the lateral wall of nose-pharynx cavity became necrotic with exudates and increased in density irregularly, especially on the right side. Few bone deformation could be seen at right maxillary sinus and nasal right lateral wall. On May 31, 2012 in the same hospital, biopsy from the right side of the nasal cavity indicated NK/T lymphoma of nasal type with the following features:

a. Nasal membrane epithelial cells revealed necrosis and exudates.
b. Clear cells proliferated and nuclear cleavage occasional found.
c. CD3 positive and much more obvious than CD20 positive cells.
d. CD56 positive.
e. CD34 and CD68 negative.
f. Ki-67 positive cells accounted for 30%.

Parenteral thiamin 100 mg plus an ampule of vitamin B complex (containing VB1 10 mg, VB2 2 mg, Niacinamide 30 mg, VB6 2 mg, pantothenic acid 1 mg) twice a day were suggested through international phone by this author, June 2, 2012. General feeling improved and nasal signs were diminished gradually within 10 days. Thereafter, the doses were doubled for 4 months. Patient became free from nasal signs and fever and returned farming and driving. Then a laboratory test revealed great improvement. Unfortunately, these tests were done in another hospital, Tianjin First Central Hospital, and failed in having the record. The patient erroneously believed to be well cured and discontinued parenteral vitamins for 3 months because nobody helped him to inject except for himself. Totally, patient was free from signs for 7 months during and after discontinuation of thiamin therapy.

Nasal signs then returned with fever and the patient admitted the Tianjin People's Hospital for radio- and chemotherapy, January 5 - 15, 2013. Computed tomographic study demonstrated no metastasis and the nasal malignancy unchanged in size, "neither larger, nor smaller". He received radiotherapy for 5 days and also daily cyclophosphamide, epirubicin, Vincristine and prednisolone for another 5 days. Within the second month after discharge, his oral palate entirely perforated. He became extremely powerless and confined in bed until his death, Jun 29, 2013, although the nasal mass reduced a little.

Discussion

Look back for the case

1. The author felt very sorrowful for no body had taken care to help him for injection, complying therapeutic schedule and frequent communication. Therefore, when he received "normal test results" from Tianjin First Central Hospital, he gave up the therapy for 3 months until signs returned because he was eager to get rid of the troublesome self-injection. Then he was obliged to admit Tianjin People's Hospital for radio- and chemotherapy, which ruined his oral plate at the second month and end his life at the sixth month. This created a very sharp contrast: thiamin, life saving; radio- and chemotherapy, lethal.

2. It was unwise to start with parenteral thiamin 100-200 mg twice a day and should be injected 300-400 mg twice or thrice daily at the very beginning with a duration about 6 months according to the clinical response.

Clinical basis of thiamin therapy

1. Thiamin therapy is based on personal clinical observation in a population with inadequate food and terribly hard labor 1958-1962 [1]. In 1959, intra-mass injection of thiamin was found dramatically effective to eradicate submandibular gland cysts, Baker's cyst, lipoma and much better than their surgical removal.

   A housewife of 40 fainted on the ground when rising up from squatting position and her right arm fractured. Within 3 months, the wound developed into an osteosarcoma with its circumference of 30 cm. Immediately close to the surface of the mass, thiamin 300

mg was infused subcutaneously for only one time. The circumference drastically reduced to 20 cm in 2 days, equivalent to a reduction of 50% in volume of the mass as calculated according to circumflex law [2]. Unfortunately, there was no more thiamin for her and also no way for further study because everything was under very rigid control.

2. In this same population, about 40% of laborers over 5 years of severe labor were found to have enlarged lymph nodes in the armpit and groin [3]. This encouraged people to consider a possible linkage between malnutrition and lymphoma as seen in osteosarcoma. Thus, lymphoma was tried.

Role of thiamin in cancer formation

1. **"Oncogenic":** According to Cascante., *et al.* [4], excessive thiamin had been considered as oncogenic. And Boros., *et al.* [5] suggested to develop anti-thiamin therapy for cancer. These were exactly and completely opposite to the truth as seen in our clinical practice ever since 1959 [6].
2. **Oncotherapeutic:** Recently, thiamin of large dose had been confirmed to be cancer therapeutic by Zastre [7], Sweet [8], Hanberry [9], Luong and Nguyen [10]. They demonstrated that high-dose thiamin decreased proliferation in a mechanism similar to that of dichloroacetate (a new anti-cancer medicine) in SK-N-BE (pancreatic cell line) and Panc-1 cells (neuroblastoma cell line). Both thiamin and dichloroacetate have the following therapeutic effects:

a. Reducing: a. pyruvate dehydrogenase phosphorylation, b. mitochondrial membrane potential, c. glucose consumption and lactic acid production, d. reactive oxygen species production.

b. Inducing caspase-3 mediated apoptosis.

As pointed by Hanberry, these findings described a potential mechanism by which high-dose thiamin reduced in vivo tumor growth. Treatment regimens with high-dose thiamin may be a safer more tolerated alternative to dichloroacetate supplementation. Future work will need to establish the role of thiamin homeostasis genes in the dose-response. These become the second solid theoretic basis of thiamin therapy for this author.

Thiamin was proved a cancer protector

The following dietary case-control reports supported that VB1 is beneficial in preventing cancer as described in the following references.

In a study of 1,207 colorectal cancer cases and 3,521 controls, Tuynes [11] found that thiamin was associated with a relative risk reduction of 0.62 (95% confidence interval 0.50 - 0.78) for colon cancer and 0.73 (95% confidence interval 0.57 - 0.94) for rectum cancer.

Slattery., *et al.* [12] studied 1,993 colon cancer cases and 2,410 controls and found that colon cancer risk was inversely associated with the intake of vegetables, whole grains, and some vitamins including thiamin, pyridoxine, and niacin.

In a study of 180 cases of colorectal cancer and 180 controls of the same sex and age range, a consistent inverse association between cancer occurrence and the intake of retinol, thiamin, carotene, vitamin C and vitamin E was confirmed by Jedrychowski., *et al* [13].

Du., *et al.* [14] found evidence that thiamin prevented prostate cancer in 102 case-control pairs. The multivariate adjusted odds ratio was 0.029 (95% confidence interval 0.009 - 0.09) as analyzed by matched t-test and conditional logistic regression.

In a study of 1,031 cases of epithelial ovarian cancer and 2,411 controls, Bidoli., *et al.* [15] concluded that the intakes of micronutrients, including thiamin, in vegetables and fruits of the subjects were inversely associated with the occurrence of ovarian cancer.

Ireson, Conway and Schwarzenbach [16] reported the effect of yeast on Ehrlich ascites tumor in mice. They fed 0.1 ml yeast to each of 80 mice of equal sex and 0.1 ml saline to another 80 mice of equal sex. After 14 days of feeding, Ehrlich ascites tumor cells were injected

into the abdominal cavity. Abdominal fluid and its cellular count were then measured at the 7th day and the 14th day after inoculation. The average abdominal fluid volumes and cellular counts in yeast group were lower than those of the saline group by 37% and 53% after 7 days, and by 30% and 40% after 14 days. When injected the tumor cells into the groin of each mouse and weighed the solid tumors of at the 14th, 21st and 28th days after inoculation. The average tumor weights of 20 mice in each of the 3 yeast groups were 30%, 13%, and 9% lower than their corresponding saline groups. Since yeast is a major medicine in beriberi therapy, these results were applicable to the role of thiamin deficiency in cancer formation.

In a study of aberrant crypt foci (ACF), a biomarker of colon cancer in rats, Bruce., *et al*. [17] found that reduced thiamin in diets increased the number of ACF in colon of the rats. They fed sucrose-based diets containing thiamin 4.9, 1.6, or 1.0 mg/kg to 16 rats as controls, and 10 rats in each of two study groups. After 160 days, the average numbers of ACF were 1.14 +/- 1.17 and 2.60 +/- 1.02 for the two study groups.

Possible mechanism of thiamin deficiency on cancer formation

When thiamin is deficient, the activities of thiamin-dependent enzymes for transketolation, decarboxylation and dehydrogenation involved in glycolysis decrease. Some intermediates in carbohydrate metabolism may be accumulated due to metabolic blockage in different pathways, such as glycolysis bypass, acetone metabolism, and amino acid breakdown and/or removal failure. For example, the triose phosphates formed by normal glycolysis will rearrange their structure to form α-oxoaldehydes.

Thiamin deficiency also decreases glutathione concentration in blood cells and heart and thereby anti-oxidant activity for free radicals and detoxifying ability for α-oxoaldehydes decreases. Some metabolites would be excessively accumulated including reactive oxygen species, reactive nitrogen species, α-oxoaldehydes, advanced glycation end-products (AGEs) and some other detrimental substances in body fluids or some tissues [18]. They may be oncogenic:

a. Prolonged elevated cellular free radicals may activate signal transduction pathways, including AP-1 and NFκB, leading to the transcription of genes involved in cell growth. They also cause DNA damage, mutation, and modification of gene expression [19]. When bone fracture, large amounts of free radicals are generated [20]. This might be the case in our osteosarcoma patient previously reported.

b. α-oxoaldehydes are also reactive compounds and adversely involved in multiple major pathologic processes, including glucose auto-oxidation, DNA oxidation, lipid peroxidation, glycation with free amino groups of proteins and free radical formation [21]. They react with proteins forming adducts and DNA causing miscoding, point mutations and cytogenetic damages. If DNA damage cannot be repaired, cancer development would be likely.

c. After treating Wistar rats with N-methyl-N'-nitro-N-nitrosoguanidine, Takahashi., *et al.* [22] found glyoxal promoted the occurrence of adenocarcinoma in the pylorus of the glandular stomach, while methylglyoxal enhanced the incidence of hyperplasia in the pylorus of the rats. Nagao., *et al.* injected methylglyoxal subcutaneously to the rats and caused tumor at the injection site.

d. The highly reactive α-oxoaldehydes may react with proteins to form possibly genotoxic compounds, AGEs, such as N-(epsilon)-carboxymethyl) lysine, pentosidine and some else. AGEs might be involved in the enhanced cancer development in advanced kidney diseases [23].

Thiamin improves the anti-oxidant activity of glutathione system and thereby reduces free radicals. Practically, thiamin might be an indirect antioxidant. Thiamin suppressed the formation of methylglyoxal [24] and the production of AGEs in bovine retinal and human umbilical vein endothelial cells cultured under high glucose condition [25]. Its inhibitory effect on AGEs formation was even stronger than that of aminoguanidine. Therefore, thiamin may be critically important in preventing some aging related diseases, including cancer, hypertension, diabetes, arthropathy, cognitive disorders, etc.

As postulated by Thornalley, Brownlee [26], Hammes., *et al.* [27], Obrenovich and Monnier [28], thiamin blocks three major pathways of hyperglycemic damage and prevents diabetic complications. These include the hexosamine pathway, the AGEs formation pathway, and the diacylglycerol-protein kinase C pathway as well as the inhibition of hyperglycemia-associated NFκB activation. Their hypotheses indicate that pathological lesions caused by thiamin deficiency would be much more numerous than those described in classic beriberi.

Preliminary suggestion of thiamin therapy

1. Large dose of parenteral thiamin should be used. It should be injected 100 - 500 mg twice or thrice daily for several months depending on patients' condition, clinical response, and the degree of malignancy of the mass. Vitamin B complex is used only for minimizing possible imbalance among B vitamins, not a routine.
2. Keep away from radio- and chemotherapy. Cyclophosphamide must be forbidden Steroids should not be used even for Hodgkins' disease because it has been widely abused causing millions of femur head necrosis in China.
3. For body surface cancers, thiamin 300 - 500 mg can be infused immediately close to and around the cancer 1 - 3 times a day. Benign tumors can be intra-mass injected.
4. Intra-cyst injection should be used for cysts on the body surface. For large cyst inside the body such as ovary cyst, prolonged intramuscular thiamin 300 - 500 mg twice or thrice a day should be curable. Intravenous thiamin may be used but not routine. Frequent dripping should not be encouraged. Oral thiamin is not useful. Benfotiamine is said as effective as thiamin injection, however, clinical study is required.
5. Oral niacinamide or niacin of 500 mg a day is required for patients with long term VB1 injections because niacin excretion may increase.

Conclusion

This case is a sharp contrast for thiamin therapy vs radio- and chemotherapy for NK/T lymphoma of nasal type. Failure of thiamin was due to poor care for the patient and multiple interfering from oncologists with traditional ideology.

Conflicts of Interest

No conflicts of interest to anybody at any aspect.

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