Reversal of Signs and Symptoms of a B-Cell Lymphoma in a Patient Using Only Low-Dose Naltrexone

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T.M. is a 61-year-old man with a medical history significant for type 2 diabetes mellitus, rheumatoid arthritis, hypothyroidism, and hyperlipidemia. For these, he had been prescribed (via physicians other than the authors) levothyroxine, metformin, glyburide, and fenofibrate. Regarding the diagnosis of follicular lymphoma, T.M. first presented to his primary care provider in April 2004 complaining of enlarged bilateral cervical and inguinal lymph nodes. Shortly before he noticed the lymph nodes, T.M. had experienced a period of profound situational stress followed by a case of Bell palsy.

In June 2004, after an initial workup, histological examination of an excised left cervical node revealed follicular lymphoma, grade 1/3 with focal areas of grade 2/3, bcl-2 positive. T.M. was promptly referred to medical oncology by his primary physician, and a chemotherapeutic regimen was prescribed. Fearing the side effects, T.M. declined treatment. The medical oncologist offered no other therapeutic options except for observation. T.M. remained symptomatic with noticeably enlarging lymph nodes.

On November 28, 2005, 17 months after the initial medical presentation and 15 months after diagnosis, T.M. presented to the Integrative Medical Center of New Mexico (medical office authors B.M.B. and A.J.B.). There, T.M. revealed a chief complaint of multiple large and enlarging cervical and inguinal lymph nodes. Physical examination revealed the greatest dimension of the largest cervical node (left side) at approximately 7.62 cm and that of the left inguinal region at approximately 12.7 cm. The latter node was particularly symptomatic and painful.

The positron emission tomography (PET)/computed tomography (CT) imaging from December 13, 2005, read as follows:

> Significant hypermetabolic uptake area seen in the cervical region, left greater than right [Figure 1]. Bilateral, pathologically active lymph nodes seen in both axillae. There is also a large area of uptake seen in the left groin, likely a lymph node [Figure 1]. There is also a smaller node in the left groin/internal iliac chain, also pathologic. There is also area of uptake seen in the left anterior chest wall at the level of the inferior border of the heart, possibly related to either a small lymph node or some inflammation.

Although this was a generally low-grade disease, radiological staging was at stage III. The author (B.M.B.) advised the patient to follow the conventional oncological recommendations; T.M. again refused. Nonconventional approaches were then discussed, including therapy with low-dose naltrexone (LDN), 3 mg every night at bedtime. Although only anecdotal evidence and case reports supported this therapy, it carried a low side effect profile with simple dosing. T.M. consequently opted to start this therapy, and the prescription was written.

B.M.B. opted for this treatment regimen based on his previous successful experience with other patients who had terminal cancer diagnoses and were thus deemed untreatable by their oncologists. The protocol was initially based on reports from Bernard Bihari, MD, and his Web site, www.lowdosenaltrexone.org. In addition to the LDN therapy, T.M. was prescribed a specific diet and a regimen of oral nutritional supplements. Ultimately, T.M. was noncompliant with the dietary advice and declined oral nutritional supplements.

Of note, he did complete 9 treatments with intravenous α-lipoic acid (ALA) in the first week following his initial appointment with B.M.B. He did not continue his intravenous ALA program but did remain compliant with the LDN (his wife ensured this compliancy). In a previous publication describing the long-term survival of a patient with metastatic pancreatic cancer,[1] ALA was a key component in the treatment

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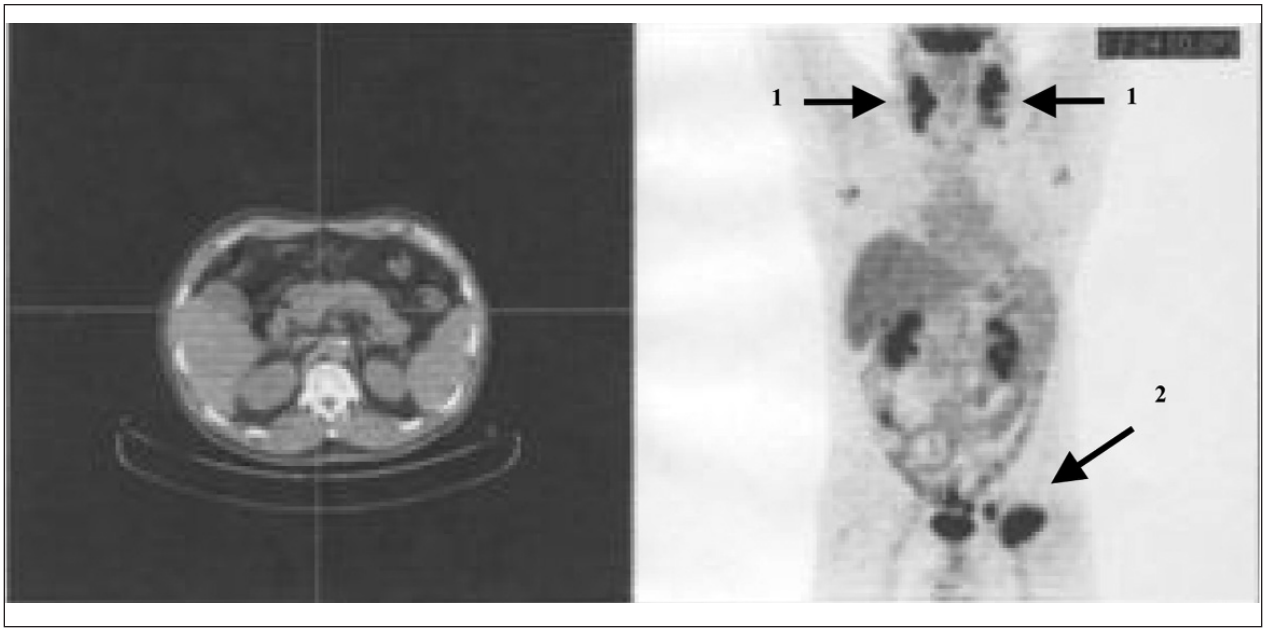

Figure 1 Computed tomography/positron emission tomography scans of December 13, 2005, demonstrate large bilateral cervical lymphadenopathy (arrows 1) and large left-sided inguinal node (arrow 2).

regimen. This patient with pancreatic cancer is still alive and free of symptoms at the date of this writing, and he remains compliant with all components of his therapeutic regimen. Interestingly, T.M. was compliant only with LDN over the 6-month period of this report.

T.M. returned to the office 1 week after starting nightly LDN. A review of symptoms at that visit revealed less pressure sensation in the cervical lymph nodes or complete resolution of the pain with a decrease in the size of inguinal nodes; the latter was confirmed by physical examination. At the 6-week follow-up, the large cervical lymph node was notably smaller as was the large inguinal node, which had then decreased to approximately 7.6 cm (originally 12.7 cm). At the 6-month follow-up on May 2, 2006, T.M. stated that his nodes had almost completely resolved, and on examination, neither the large cervical nodes nor the large inguinal nodes were palpable. Follow-up CT/PET imaging from May 16, 2006, revealed significant interval improvement in the abnormal foci of activity seen in the neck, axillae, and groin. No foci of abnormal radiotracer activity were identified on this study (Figure 2). T.M. did not follow up in the office after the 6-month visit nor the second CT/PET scan, but at a 1-year telephone follow-up, he reported that he remained symptom free.

Follicular Lymphoma

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma and the second most common lymphoma in the United States. It is a lymphoma of the follicle center B cells (centrocytes and centroblasts) usually with a predominance of centrocytes. The World Health Organization classification grading system for FL is based on the number of centroblasts per high-power field.[2] Grade 1 and 2 FLs are considered indolent lymphomas. Grade 3a may also be an indolent tumor, while grade 3b is considered more aggressive.[2]

Clinically speaking, the median age at diagnosis is 60 years, and it affects men and women equally. Initially, the patient usually notices painless cervical, axillary, inguinal, and femoral lymphadenopathy; hilar and mediastinal nodes may be present. The course of FL varies among patients. Some patients exhibit waxing and waning of the disease for years without the need for medical therapy. Less fortunate patients present with highly aggressive and disseminated disease that requires urgent treatment because of massive lymph nodes or organ enlargement, which causes pain and/or lymph and organ obstruction. Based on this potential clinical course of low-grade FL, it is theoretically possible that T.M.'s nodes spontaneously resolved. However, the rapid and total resolution of pathologic nodes based on physical examination and on PET/CT imaging suggests that LDN had a large part to play in our patient's impressive recovery, thus prompting this report.

Despite many changes in therapeutic approaches, overall survival and disease-free intervals have not

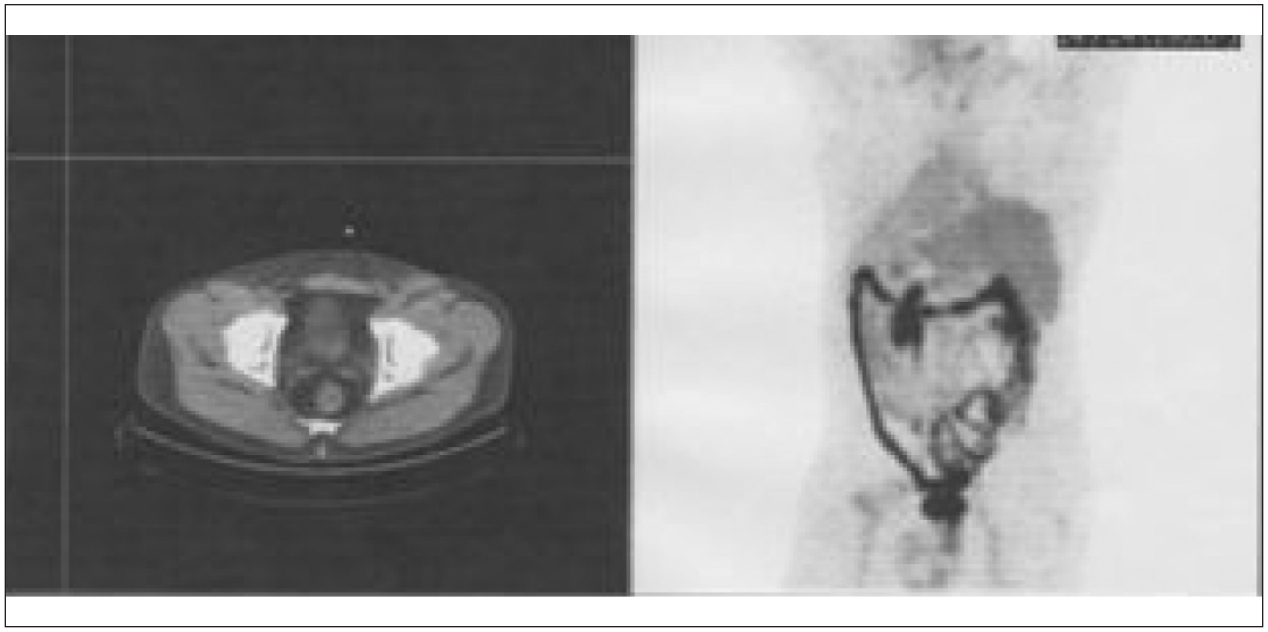

Figure 2 Computed tomography/positron emission tomography scans of May 16, 2006, demonstrate significant interval improvement of disease as compared with those of December 13, 2005.

changed much over the years with regard to FL. Conventional medicine considers FL incurable. Median survival is 9 years after diagnosis, often with many cycles of remission and relapse, and most patients eventually die from their disease. Various chemotherapeutic regimens have yet to demonstrate definitive survival advantages and are laden with frightening, unsavory, and occasionally fatal side effects. Studies on other therapeutic options (ie, monoclonal antibodies, radiation therapy, and interferon/ribavirin) have suggested possible efficacy.[3] External-beam radiotherapy, specifically, has shown potential in curing grade 1 or 2 FL.[4] Recently, CHOP chemotherapy with rituximab, followed by rituximab maintenance, has shown some overall survival advantage.[5]

In this particular case, our patient adamantly refused chemotherapy, and no other options were offered. Thus, he sought an alternative opinion. Because of the patient's refusal to accept standard medical treatment, other options were considered.

Low-Dose Naltrexone

Naltrexone is a pharmacologically active opioid antagonist. In conventional medicine, naltrexone is used to treat opioid and alcohol addiction, usually at doses of 50 mg or higher.

At very low dosages, naltrexone has been found to have immunomodulating properties.[6] As such, LDN (3.0-4.5 mg per dose) was first used by Bernard Bihari, MD, as a therapeutic agent for people with AIDS.[7] Given this immunomodulatory activity, LDN has been proposed for use in people with malignancies, multiple sclerosis, and autoimmune diseases. A recent publication by Smith et al[8] at the Pennsylvania University College of Medicine showed a marked improvement with an excellent safety profile in active Crohn disease using LDN.

Behind the anticancer mechanisms of LDN lies Bihari's 3-fold mechanistic approach: that nocturnally dosed LDN may cause an increase in (1) metenkephalin (an endorphin produced in large amounts in the adrenal medulla) and β endorphin in the blood stream; (2) the number and density of opiate receptors on the tumor cell membranes, thereby making them more responsive to the growth-inhibiting effects of the already present levels of endorphins, which in turn induces apoptosis in the cancer cells; and (3) the absolute numbers of circulating cytotoxic T cells (CD8+/T_H1) and natural killer (NK) cells, as well as NK cell activity.[9,10] In addition, recent studies suggest that a molecular cousin of naltrexone, methylnaltrexone, can inhibit angiogenesis.[11] This could be another important potential mechanism in hampering tumor growth. Naltrexone does undergo an extensive hepatic first-pass metabolism wherein methylation plays a role.[12]

Bihari reported that he has used LDN with promising results for people with various malignancies including but not limited to primary cancers of the bladder, breast, liver, lung, lymph nodes, colon, and

rectum. Over the years, he has administered LDN to more than 450 people with cancer, most of whom initially failed standard conventional treatments. According to Bihari, 86 of the 354 patients followed regularly demonstrated at least a 75% reduction in overall tumor bulk, and an additional 125 patients demonstrated disease stability.[9] An early study by Zagon and McLaughlin[12] showed that very-low-dose naltrexone slowed the growth of neuroblastoma cells in culture, suggesting a role of the medication in the treatment of certain cancers. These researchers later suggested that this modulation of cancer cell growth in tissue culture may be via a different pathway than simple alterations in apoptosis or necrosis.[13] Other researchers, such as Lissoni et al,[14] reported on the treatment of malignant astrocytomas with naltrexone plus radiotherapy, which demonstrated a significant survival benefit when compared with radiotherapy alone.[14]

Discussion

This case report describes the treatment of a 61-year-old man with biopsy-proven FL. His initial physical examination and PET/CT scan showed multiple large, metabolically active, pathologic lymph nodes that impressively demonstrated complete resolution within 6 months of commencing therapy with nocturnally administered LDN. This case not only suggests the potential role of LDN in the treatment of FLs but also highlights the ease of maintaining compliance with this therapeutic regimen. In addition, T.M. was prescribed a healthy diet, a nutritional supplement regimen, and intravenous ALA. He did not remain compliant with any of these 3 modalities. Thus, in this case study, we are choosing to attribute T.M.'s impressive achievement of clinical and radiological remission to the LDN alone.

At the time of this report, and per telephone communication from the patient's wife, T.M. remains asymptomatic from his disease, now 1 year after his last CT/PET imaging. T.M. remained on LDN for 6 months only; he stopped taking it in June 2006. Perhaps these results represent a period of spontaneous remission in the potential waxing and waning course of his follicular lymphoma. However, given the rapidity of the nodal waxing, its equally rapid dimensional wane and the summarily low cost of the medication, its ease of administration, and possibility for efficacy, LDN deserves further investigation.

We believe that by the mechanisms presented herein, LDN demonstrates significant potential to increase disease-free as well as overall survival in people with FL. It is hoped that biomedical science will soon develop cures for the currently incurable cancers, perhaps via gene therapy, cancer vaccines, or other biological platforms. Until that time, we need to consider treatments that have the potential to alter the course of cancers for the better. Especially needed are treatments such as LDN that are inexpensive, demonstrate ease of compliance, and are bereft of the side effects plaguing most currently used conventional therapies.

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