CASE STUDY: **PROSTATE ADENOCARCINOMA**

-Enzyme Therapy Protocol-

ABSTRACT

Plant extracts with a high content of proteolytic enzymes have been used for a long time in traditional medicine. The therapeutic use of proteolytic enzymes is partly based on scientific studies and is partly empirical. Studies have shown that enzyme therapy can be used as an adjunct in oncology as it can reduce the adverse effects caused by radiotherapy and chemotherapy. There is also evidence that, in some types of tumors, survival may be prolonged. The beneficial effect of systemic enzyme therapy seems to be based on its anti-inflammatory potential. However, the precise mechanism of action of systemic enzyme therapy remains unsolved. Furthermore, there are numerous alterations of cytokine composition during therapy with orally administered enzymes, which might be an indication of the efficacy of enzyme therapy. Effects on adhesion molecules and on antioxidative metabolism can also provide reasons to use proteolytic enzyme therapy in oncology. These properties such as anti-inflammatory, antioxidant, reduction of adhesion molecules, and prolonged survivability makes proteolytic enzyme therapy a viable adjunct in oncology for conditions such as prostate cancer. In this case study we apply a high-dose proteolytic enzyme blend from Transformation Enzyme Corporation named Transformation Professional Protocol™ (TPP) Protease in powder form to a diagnosed 71yrs. old male with Prostate Adenocarcinoma.

INTRODUCTION

Prostate cancer is the most common non-cutaneous cancer in men worldwide, with an estimated 1,600,000 cases and 366,000 deaths annually. Despite recent progress, prostate cancer remains a significant medical problem for the men affected, with overtreatment of inherently benign disease and inadequate therapies for metastatic prostate cancer. Here we attempt to support such a diagnosis with proteolytic enzymes known for their anti-inflammatory, antitumorigenic, antimetastatic, anticoagulative, and fibrinolytic properties.

For example, recent results from preclinical and pharmacological studies recommend bromelain as an orally given drug for complementary tumor therapy: bromelain acts as an immunomodulator by raising the impaired immune-cytotoxicity of monocytes against tumor cells from patients and by inducing the production of distinct cytokines such as tumor necrosis factor-alpha, interleukin -1b, Il-6, and Il-8. Bromelain is one of many proteolytic enzymes that exist in nature which have been shown to benefit the cellular terrain when combating tumor cell growth as depicted in *Table 1* and because of these benefits we are applying proteolytic enzymes in this case study.

Table 1. *Bromelain effects, in vitro (BP, F4, F5, F9) and in vivo (POS), on tumor cell growth and metastasis.*

Protease	Parameter	Effect Significance
Bromelain BP Bromelain F9 46	tumor cell proliferation	reduction of tumor cell growth
Bromelain BP Bromelain F4, F9 Bromelain F5	tumor cell invasion through extracellular matrix	reduction of invasive potential of tumor cells
Bromelain POS	growth of lung metastases in mice	reduction of metastatic potential of tumor cells
Bromelain BP Bromelain F9	CD44 expression on metastatic cells	reduction of tumor cell adhesion to endothelial cells
Bromelain BP	growth of lung metastasis in mice	reduction of metastatic potential of tumor cells
Bromelain BP	survival time of mice bearing lung metastases (in vitro A in vivo)	mouse survival time

Bromelain BP (base powder), commercial crude extract; POS, BP given orally; F4, F9, Bromelain fractions.

Anatomically, the human prostate contains three zones: the peripheral zone, where ~60%–75% of prostate cancers arise; the central zone; and the transition zone. Studies have demonstrated that both luminal cells and basal cells can serve as the cell of origin for prostate cancer. Overexpression of oncogenes such as myrAKT1 transforms normal human prostate epithelial cells into prostate cancer cells, which display prostate adenocarcinoma and squamous cell carcinoma phenotypes. Malignant transformation of the prostate follows a multistep process, initiating as prostatic intraepithelial neoplasia (PIN) followed by localized prostate cancer and then advanced prostate adenocarcinoma with local invasion, culminating in metastatic prostate cancer.

The Gleason grading system, which was originally defined by Donald Gleason based on histological patterns of prostate adenocarcinoma, has been refined over the years and is the most widely used grading system defining prostate cancer aggressiveness. Since a central feature of prostate cancer is its hormone responsiveness, androgen deprivation therapy (ADT) using agents that block the androgen pathway is now the standard of care for prostate cancer. Resistance to ADT can develop, resulting in primary castration-resistant prostate cancer (CRPC) or metastatic CRPC (mCRPC). The treatment of prostate cancer depends on grade, stage, and age and ranges from active surveillance to a mix of surgery, chemotherapy, radiation, and/or ADT.

Localized cancers are stratified into three groups of low, intermediate, and high risk based on Gleason score. Low-risk cancers (Gleason 3 + 3) are typically managed by active surveillance and at the other end of the spectrum are high-risk cancers (Gleason ≥8), which receive more aggressive treatment, including surgery and radiation-based therapies. A major treatment decision challenge in prostate cancer lies with intermediate-risk disease (e.g., Gleason 3 + 4), as these patients exhibit considerable differences in outcomes. For patients who do receive treatment for localized prostate cancer and experience disease recurrence (defined by rising PSA), ADT is commonly used in combination with surgery or radiation.

In the setting of metastatic disease, the initial treatment plan includes ADT, often with chemotherapy. ADT can involve two approaches: surgical castration or, more commonly, chemical castration with drugs targeting AR signaling regulated by the hypothalamic–pituitary–testicular axis. Although most patients initially respond well to ADT, recurrence occurs in virtually all cases, leading to mCRPC.

CASE STUDY

In this present case study, we have a 71-yr-old male with a diagnosis of Prostate Adenocarcinoma confirmed by biopsy, MRI, and elevated PSA. The patient's family history includes prostate cancer for his father and brother. Father died of a heart weakened by radiation received for prostate cancer in the early 1990's. The patient denies any allergies to drugs, foods, or environmental triggers and has unremarkable past medical history. The patient states he feels well and has no symptoms. He is willing to make lifestyle changes and comply with our recommended protocol for his condition identified as a tumor. His immediate concerns are the tumor on his prostate and the stress he is getting from his wife's worrying as she has PTSD and can't help it at times.

The goal of our protocol is to reduce the prostate tumor significantly, bring PSA levels to normal <4ng/mL, eliminate the large pelvic lymph nodes, and reduce the Detrusor muscle hypertrophy observed in the bladder upon MRI.

INITIAL MEDICAL RECORDS 10/07/22 provided by the patient:

PSA: 336 ng/mL

Hs CRP: >10mg/L

MRI REPORT 11/08/22 with and without contrast on high field 3.0 Tesla showed:

Prostate volume: 51 .69 cc

Prostate dimensions: 5.2 x 5.2 x 3.9 cm

Transition Zone: Central gland hypertrophy and large tumor measuring 15x29x30mm (APxMLxCC) at the posterior apex and mid prostate gland. The lesion extends posteriorly and inferiorly from the prostate capsule and is in close proximity to the anterior low rectum.

Peripheral Zone: In the right mid posterior peripheral zone there is a markedly hypointense ADC signal measuring 14x8x12mm and increase permeability.

Seminal Vesicles: the seminal vesicles are normal and symmetrical bilaterally.

Extracapsular extension: the bilateral neurovascular bundles are not well defined and underlying invasion is within the differential.

Bladder: there is detrusor muscle hypertrophy.

Lymph Nodes: Mildly enlarged oval-shaped lymph node in the right pelvic sidewall measuring 9x7mm with a few other smaller lymph nodes also identified at this location.

Other: heterogenous hypointense lesion measuring 11x10mm at the right pubic symphysis.

BIOPSY REPORT 12/14/22:

Site A: No. of cores: 1; Dimensions: 13 mm (left lateral base)

Diagnosis Summary: PROSTATIC ADENOCARCINOMA; Gleason Score 7(4+3); 1 of 1 core involved; Tumor measures 7 mm in length; Microscopic Description: 90% of Gleason pattern 4.

Site B: No. of cores: 3; Dimensions: 10,6,4 mm (left lateral mid)

Diagnosis Summary: PROSTATIC ADENOCARCINOMA; Gleason Score 8(4+4); 3 of 3 cores involved; Tumor measures 13 mm in length; Microscopic Description: 100% of Gleason pattern 4.

Site C: No. of cores: 2; Dimensions: 20,11mm (left lateral apex)

Diagnosis Summary: Benign soft tissue. No prostatic glands present.

Site D: No. of cores: 1; Dimensions: 14 mm (right lateral base)

Diagnosis Summary: PROSTATIC ADENOCARCINOMA; Gleason Score 8(4+4); 1 of 1 core involved; Tumor measures 13 mm in length; Microscopic Description: 100% of Gleason pattern 4.

Site E: No. of cores: 1; Dimensions: 13 mm (right lateral mid)

Diagnosis Summary: PROSTATIC ADENOCARCINOMA; Gleason Score 8(4+4);1 of 1 core involved; Tumor measures 13 mm in length; Microscopic Description: 100% of Gleason pattern 4.

Site F: No. of cores: 2; Dimensions: 10,8 mm (right lateral apex)

Diagnosis Summary: PROSTATIC ADENOCARCINOMA; Gleason Score 8(4+4); 2 of 2 cores involved; Tumor measures 12 mm in length; Microscopic Description: 100% of Gleason pattern 4.

Case Comments: Large cribriform glands present. This case has been reviewed in an Intradepartmental conference and all participating pathologists agree with the above diagnoses.

PROTOCOL

Upon initial consultation on 12/07/22, the patient had already been diagnosed by his Oncologist and provided lab testing and biopsy as shown above. The patient had begun taking a set of supplements when he learned of his diagnosis to start fighting his war against cancer. He was allowed to stay on several of them as I didn't see any contraindications with my protocol, and I didn't want to affect his belief in what he had started.

After consent and consultation, the patient was recommended a treatment protocol of 2 caps TPP Protease IFC between meals 3 x day, 1 tsp TPP Protease powder between meals 3 x day (15 grams), 1 full dropper L-Drain in 8 oz glass 3 x day, 1 cap TPP Probiotic 42.5 in the morning, and 1 cap TPP Probiotic 42.5 at night along with a diet which excluded GMO's, gluten, dairy, and any artificial processing. The patient was recommended Transformation's **Thrive in 63™** wellness program which consists of an organic, whole, and all-natural diet plan with a low glycemic index.

The following provides the ingredient content of each supplement used in this case study from Transformation Enzyme Corporation:

TPP Protease powder - Tzyme™ Protease Blend (peptidases, bromelain): 355,020 HUT + 19 SAPU (600,000 PU) in every 492 mg. Assuring optimal protein digestion and proper blood flow is necessary for effective nutrient delivery, a healthy immune response, and the body's natural detoxification processes. This systemic protease formulation includes over 355,000 HUT units of protease activity in every 492 mg serving supporting healthy circulation (blood and lymph) and optimal immune health. Supporting circulation with Protease encourages delivery of oxygen and nutrients to the cell for health and vitality, removal of metabolic wastes from the cell, and transport of immune cells throughout the body to help maintain a healthy internal environment. Optimal circulation is dependent upon the

presence of effective proteolytic enzymes. Endo/exo peptidases are known to break the inner/terminal bonds of amino acid chains for more efficient hydrolysis of proteins. The highly active systemic enzymes in this formula have a wide range of pH stability (3.0 pH – 10.0 pH) which is essential for maximum benefit. Bromelain is a group of soothing plant enzymes which help promote improved protein digestion and healthy elimination as well as overall cardiovascular, muscular, urinary, and immune system health.

TPP Protease IFC - Vitamin A (100% as beta carotene): 2,370 mcg (7,900 IU) (263% DV), Vitamin C (as magnesium ascorbate): 9 mg (10% DV), Vitamin E (as d-alpha tocopheryl succinate): 1.3 mg (2 IU) (9% DV), Zinc (as zinc citrate): 0.5 mg (5% DV), Selenium (as selenium citrate): 16 mcg (29% DV), Tzyme™ Protease Blend (proteases, bromelain, papain): 209 mg (2,800,000 FCCPU + 65,400 HUT), Tzyme™ AntiOx Blend (Kelp, Irish moss, Rutin, Grape seed extract, Quercetin, Alpha-lipoic acid, Citrus bioflavonoid complex, Rose hips (fruit), Hesperidin complex, Turmeric (root), Asian ginseng (root), Eleuthero (root), Gingko biloba leaf extract, L-glutathione, CoQ10, Gingko biloba leaf, Green tea extract, Catalase, Flaxseed, Lutein, SOD): 253 mg. This supplement is a highly effective formulation with enzymes, vitamins, minerals, and herbs designed to promote overall wellness for oxidative stress and is especially beneficial for inflammation, pain, and fatigue as well as to scavenge and correct oxidized molecules, helping prevent free radical damage in the body so common in states of prostate cancer.

L-Drain - Red Root extract: 9 mg, Red Clover blossoms extract: 7.5 mg, Stillingia Root extract: 7.5 mg, Prickly Ash Bark extract: 6 mg. The lymphatic system must be considered a foundational aspect for the maintenance of optimal health. Transportation throughout this network is not catalyzed by a continuous pump like the heart. Rather, it relies on the milking action of the muscles, lungs, and arteries. The lymphatic vessels are found in almost every single tissue and system of the body. L-Drain was created with the sole intent of helping the lymphatic system perform its normal daily functions. This concentrated, rapidly assimilated herbal product assists the lymphatic system and supports lymphatic flow so was important in this patient due to his MRI finding of Lymphadenopathy.

TPP Probiotic 42.5 - Tzyme™ Probiotic Blend (*Bacillus coagulans*, *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Bifidobacterium longum*, *Lactobacillus salivarius*, *Lactobacillus bulgaricus*, *Bifidobacterium infantis*, *Lactobacillus rhamnosus*, *Lactobacillus casei*): 280 mg (42.5 billion cfu), Jerusalem Artichoke tuber: 10 mg. Beneficial bacteria often become imbalanced by poor diet choices and environmental lifestyle stressors. Issues can arise when opportunistic microorganisms feed on undigested food molecules, creating gas. This carefully mixed selection of GI stable and heat stable microorganisms mirrors the ratios found in a healthy GI tract. These organisms enhance the ecological balance of friendly bacteria, benefiting digestion, elimination, and immune function by populating the gut with the “friendly” naturally occurring bacteria vital to our overall health.

The patient initially had no adverse effects or discomfort in taking 15 grams of TPP Protease powder and on 01/04/23 I recommended continuing the rest of the supplements at the same dose and only increasing the dose of the TPP Protease powder to 10 grams 3 times a day (30 grams) on an empty stomach until the end of the study on 05/17/23, which ran for a total of 23 weeks. On 02/03/23 by the direction of his Oncologist the patient began Testosterone blockers with one shot of Lupron depot and then on 02/16/23 started Zytiga with Prednisone. March 3rd, he began Orgivyx for blocking Testosterone plus Prednisone plus Zytiga and was told that with these blockers he should see PSA go down within 4 to 6 months (July to September).

FOLLOWUP

The patient finished the protocol in mid-May and began radiation at the end of May for extra security measures per his Oncologist. The patient began having challenges with urination after beginning radiation, and as adjuvant enzyme therapy has been shown to reduce radiation induced adverse effects, he took it upon himself to start the enzymes again which resolved the problem.

Our original stated goal of our protocol to reduce the prostate tumor significantly, bring PSA levels to normal <4ng/mL, eliminate the large pelvic lymph nodes, and reduce the Detrusor muscle hypertrophy observed in the bladder were all met as evidenced by the follow up MRI shown below. The patient was diagnosed to be in remission per most recent consult with Oncologist and will be monitoring PSA levels periodically.

FOLLOWUP TESTING 05/15/23:

> PSA: 0.6 ng/ml (down from 336 ng/ml on previous test, 2 to 4 months earlier than expected by Oncologist, which could be due to the mega dose of proteolytic enzymes the patient had been taking since December)

MRI REPORT 05/15/23 with and without contrast on high field 3.0 Tesla showed:

> Prostate volume: 15.54 cc (down from 51.69 cc on previous MRI)
>
> Prostate dimensions: 3.4 x 3.0 x 3.0 cm (down from 5.2 x 5.2 x 3.9 cm on previous MRI)
>
> Transition Zone: The transitional zone is low in T2 signal intensity. The central zone demonstrates low ADC signal symmetrically. If additional biopsy is indicated, the right central zone demonstrates focal moderate hypointense ADC and mild hyperintensity DWI, without increased permeability and measures greater than 1.5 cm in size (PI-RADS 3). This demonstrates no increased permeability.
>
> Peripheral Zone: Since the prior exam, the prostate is smaller in appearance with more diffuse decreased T2 signal, most consistent with post treatment change. There is persistent low signal in the posterior apex on T2-weighted imaging, without associated low ADC. By strict scoring, this likely represents a PI-RAD 2 lesion, but is at the known site of prior PI-RADS 5 lesions, consistent with posttreatment response.
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> Seminal vesicles: The seminal vesicles are normal and symmetrical bilaterally.
>
> Extracapsular extension: The prostatic capsule is preserved. The neurovascular bundles are intact. There is no evidence of tumor in the rectal prostatic angles.
>
> Bladder: Normal.
>
> Lymph nodes: The previously visualized areas of right pelvic sidewall adenopathy have resolved. No abnormally enlarged pelvic lymph nodes.
>
> IMPRESSION: PI-RADS: Category: post treatment change with visible reduction in size and restricted diffusion in the posterior apical known prostate cancer. The overall prostate size is reduced in the signal intensity is decreased nearly diffusely on T2-weighted imaging. The pelvic lymphadenopathy has also resolved. There is no focal area in the peripheral zone meeting current PIRADS 4 or 5 rating. The inferior right pubic ramus lesion appears unchanged. The central zone demonstrates restricted diffusion but appears symmetric and is indeterminant (PI-RADS 3).

DISCUSSION

Proteolytic enzymes have been researched for centuries and have evidence of many systemic benefits to our health. They have been shown to reduce tumor cell growth, reduce the invasive potential of tumor cells, reduce the metastatic potential of tumor cells, and reduce tumor cell adhesion to endothelial cells by reducing expression of CD44 molecules. CD44 is a cell adhesion glycoprotein that also governs cell signaling. Dysregulated CD44 expression characterizes most human cancers, including prostate cancer. Prostate cancer loses expression of CD44 standard (CD44s) that is present in benign epithelium and overexpresses the novel splice variant (v) isoform, CD44v7-10. It plays important roles in lymphocyte homing, inflammation, cell migration, signaling, and tumor metastasis.

Recent studies have shown that bromelain and its proteolytic properties have the capacity to modify key pathways that support malignancy. Presumably, the anticancerous activity of bromelain is due to its direct impact on cancer cells and their microenvironment, as well as on the modulation of immune, inflammatory, and homeostatic systems. In an experiment conducted by Beez et al., chemically induced mouse skin papillomas were treated with bromelain and they observed that it reduced tumor formation, tumor volume, and caused apoptotic cell death. Bromelain is found to increase the expression of p53 and Bax in mouse skin, the well-known activators of apoptosis which is needed for natural cell death. Bromelain also decreases the activity of cell survival regulators, thus promoting apoptotic cell death in tumors.

Different studies have demonstrated the role of NF-κB, Cox-2, and PGE2 as promoters of cancer progression. Evidence shows that the signaling and overexpression of NF-κB plays an important part in many types of cancers. Cox-2, a multiple target gene of NF-κB, facilitates the conversion of arachidonic acid into PGE2 and thus promotes tumor angiogenesis and progression. It is considered that inhibiting NF-κB, Cox-2, and PGE2 activity by proteolytic enzymes has potential as a treatment of cancer. Bromelain was found to downregulate NF-κB and Cox-2 expression in mouse papillomas and in models of skin tumorigenesis. Bromelain markedly has in vivo antitumoral activity for the following cell lines: P-388 leukemia, sarcoma (S-37), Ehrlich ascetic tumor, Lewis lung carcinoma, and ADC-755 mammary adenocarcinoma. In these studies, intraperitoneal administration of bromelain after 24 hours of tumor cell inoculation resulted in tumor regression.

Another property of Proteolytic enzymes is the increase of the alpha 2 Macroglobulin (alpha 2M) which aids in irreversibly attaching to proinflammatory cytokines including the Transforming Growth Factor beta (TGF-beta). The multifunctional cytokine TGF-beta which belongs to a family of polypeptide growth factors has pleiotropic effects on embryogenesis, cell growth, differentiation, tissue repair and remodeling. Three distinct iso-forms of the peptide (TGF-beta 1-3) exist in mammalian species. TGF-beta is the prototype of this family and has the ability to stimulate the activity of its own promoter via AP-1 sites, an activity which leads to a positive autocrine loop after an initial stimulus. Local overproduction of TGF-beta results in an increase in the expression of adhesion molecules, in the production of extra cellular matrix proteins, and in the proliferation of fibroblasts. Thus, profibrotic and immunosuppressive effects based on overproduction of TGF-beta are involved in several clinical conditions, which are characterized by prolonged tissue repair or chronic inflammatory reactions. Furthermore, an inhibition of the cytotoxicity of macrophages, granulocytes and natural killer- and LAK cells leads to immunosuppression, which is observed during certain bacterial and viral (HIV, HZ, hepatitis C) infections, and in cancer patients. Tumor cells as well as tumor infiltrating effector cells (macrophages, T-cells) have been shown to produce high amounts of TGF-beta.

The role of alpha 2M in reducing TGF-beta has been examined by researchers. These investigators reduced TGF-beta-stimulated collagen synthesis in liver myofibroblasts by introducing the fast form of alpha 2M. Activated alpha 2M neutralizes TGF-beta, produced by breast-cancer cells, and thereby promotes the

activation of NK, LAK and tumor-specific T-cell response by interleukin-2. Reduction of TGF-beta overproduction reduces TGF-beta synthesis. It has been described in the literature that proteases react with alpha 2M in blood, and convert the slow form into the fast form. After this reaction, alpha 2M can recognize the receptor LRP on hepatocytes, endothelial cells, fibroblasts, etc. which is responsible for the rapid plasma clearance of transformed alpha 2M, whereas the slow form of alpha 2M shows no affinity for LRP. alpha 2M in the fast form (alpha 2M+enzymes) binds TGF-beta. TGF-beta bound to the fast form of alpha 2M cannot bind to its cell receptor and this complex is phagocytized very quickly.

As these health benefits of proteolytic enzymes have demonstrated it is with great confidence that they can be used by any clinician as an adjunct in supporting cells that share characteristics of inflammation, invasiveness, metastasis, abnormal growth, and failure to induce apoptosis.

CONCLUSION

Here we have 71-yr-old patient with a diagnosis of Prostate Adenocarcinoma confirmed by elevated PSA, abnormal MRI findings, and Biopsy expressing pathology. The patient was given adjunct support along with allopathic treatment provided by his Oncologist with a protocol based on proteolytic enzymes, probiotics, and herbs to support the lymphatic system in the attempt to change the patient's cellular terrain in order to provide an environment where cancer cells can no longer survive or proliferate. All end points of reducing prostate tumor size, reducing PSA to normal levels, reducing Lymphadenopathy, and reducing muscle hypertrophy were met and the patient was confirmed to be in remission by his Oncologist.

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