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Case Study: Metastatic Colorectal Cancer Management Using the Integrated Health Clinic Approach

Introduction:

Colorectal cancer (CRC) is the fourth most common cancer in the United States, with the second highest rate of mortality. According to SEER data, the number of new cases of colon and rectal cancer was 42.4 per 100,000 men and women per year. The number of deaths was 15.5 per 100,000 men and women per year, based on 2008 -2012 cases and deaths[1]. Death rates have declined since the mid 1980's most likely due to improvements in early detection techniques and advancements in adjunctive therapies[2]. Current treatment guidelines vary greatly depending on the stage at diagnosis. Localized CRC is comprised primarily of surgical resection with en bloc lymphadenectomy. Treatment of metastatic cancer is more complex and is determined by the clinical pathologic stage. Neoadjuvant chemoradiation therapy is an important component of treatment to decrease the risk of local recurrence[3] and chemotherapy is an important treatment option for metastatic CRC. The overall survival is increased from 6 to 12 months by treatment with 5-FU and leucovorin. The addition of Irinotecan (5-flourouracil, leucovorin, irinotecan – FOLFIRI) and Oxaliplatin (FOLFOX) raised overall survival to a median of 20 months[4]. With the more recent addition of anti-VEGF and anti-EGFR monoclonal antibodies, a 3% - 5% improvement to five-year survival rates can be attained[5].

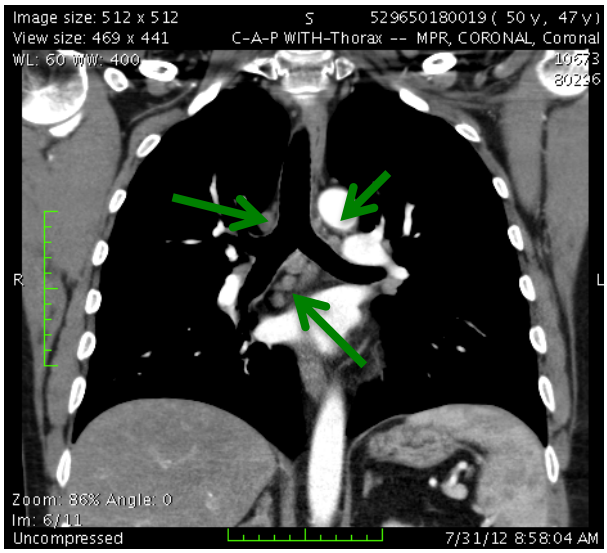
The immune system uses fever to combat illnesses ranging from bacterial infection to malignancy. Research and numerous case studies show the effectiveness of heat treatment or hyperthermia as a cancer treatment, either alone or in combination with chemotherapy and radiation[6]. The use of hyperthermia alone has shown improvements in both partial and complete response rates for several malignancies, including squamous cell cancers, adenocarcinomas and melanomas[7]. In this report, we present a case of metastatic colorectal carcinoma treated at Integrated Health Clinic (IHC), using both local and whole body hyperthermia in conjunction with disease-specific dietary, supplementary, injection and intravenous therapies. The use of hyperthermia and other treatment modalities such as intravenous vitamin C will be reviewed to show the potential use of these naturopathic interventions in the palliative care of CRC in combination with conventional treatment[8].

Case history:

D.M., a 47 year-old male from Newfoundland was diagnosed with metastatic CRC in 2010. Initial symptoms began in 2009 consisting of intermittent constipation and diarrhea, associated with right upper quadrant abdominal pain. A positive fecal occult blood test led to a colonoscopy in January 2010, which showed a stricturing lesion at the hepatic flexure of the colon. DM underwent a right hemicolectomy in January 2010, followed by chemotherapy with FOLFOX on a 14-day cycle for 6 months. An abdominal CT from September 2011 demonstrated suspicious liver lesions and two small peritoneal deposits. FOLFIRI with Avastin was initiated at this time by his medical oncologist.

In November 2011, D.M. underwent a Sugarbaker procedure with peritonectomy and resection of recurrent disease followed hyperthermic intraperitoneal chemotherapy (HIPEC) (mitomycin-C 64mg in 4.5 liters Dianeal for 90 minutes). An NMD/total body bone scan was done in December 2011 and showed a normal total body bone survey without evidence of bony neoplastic change. Reduction ileostomy was performed in February 2012. He was initially booked for infusional 5-FU/Folinic acid but was switched to Xeloda due to severe side effects. He completed 4 cycles of Xeloda by June 2012. A CT scan of the chest was done in June 2012 and showed several small nodules within the lungs. In July 2012, a repeat CT of the chest, abdomen and pelvis showed abdominal, pulmonary and mediastinal progression compared to the December 2011 scan (Figure 1.).

Fig 1. CT scan of the chest & abdomen – coronal – July 2012



DM's health status continued to worsen, experiencing roughly 20 bowel movements daily with post-prandial pain and weight loss. Prior to his initial phone consultation

at the IHC on September 13th 2012, DM's medication list included digestive enzymes, probiotics and oxycodone for pain. Treatments recommended included loco-regional hyperthermia (LRHT) 3x weekly for 6 weeks, fever-range whole body hyperthermia, IVAA, and oral targeted supplementation consisting of neutraceuticals and pharmaceuticals (Table 1).

Table 1. Treatment Protocol - Prescription and Supplements

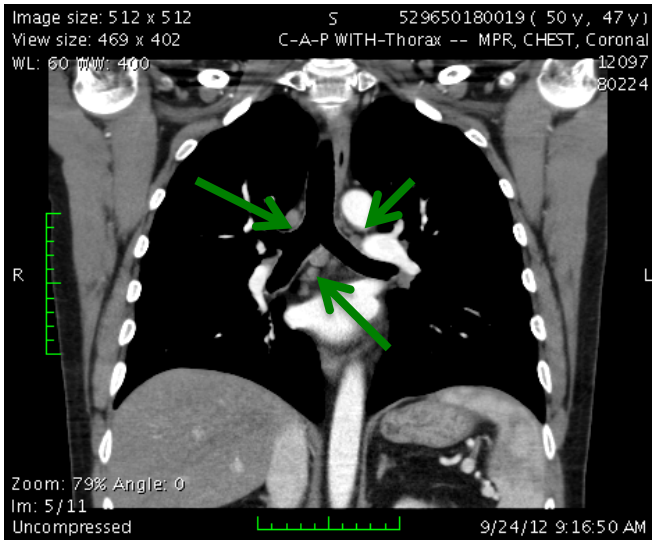
Prescriptions	**Dosage**	**Effect**
Celebrex	200mg – 400mg capsule p.o. BID	Inihibit cyclooxygenase-2 (COX2) enzymes. Blocking COX 2 decrease tumor invasiveness[9]. Induce apoptosis and inhibit angiogenesis of tumor cells[10].
Metformin	250mg tablet p.o. BID	Activation of AMPK may result from a mild inhibitory effect of metformin on mitochondrial complex 1, which in turn would raise AMP and activate AMPK[11]. Decrease insulin (promotes cancer cell growth) resistance and reduces insulin level. Direct inhibitory effect on cancer cell growth and antitumoral action[12].
Supplements		
I.V. Vitamin C	2x/week	Improve quality of life, decrease tumor size and prolong relapse interval[13]. Alleviates cancer and chemotherapy related

		symptoms[14]
Can-Arrest	2 capsules p.o. BID	Inhibition of the transcription factor NF-κB to arrest tumor growth and its progression[15]. Anti-inflammatory and antioxidant activity causing inhibition of vascular endothelial growth factor-mediated angiogenesis in human intestinal microvascular endothelial cells[16].
Cordyceps	2 capsules p.o. BID	Anti-metastatic action through inhibiting platelet aggregation induced by cancer cells and suppressing the invasiveness of cancer cells[17]. Immunomodulation resulting in tumor destruction[18].
Vitamin D	2,000 I.U. tablet p.o. BID	Increased circulating levels of vitamin D are associated with reduced occurrence and a reduced mortality in different histological types of cancer, including those resident in the skin, prostate, breast, colon, ovary, kidney, and bladder[19]. Maintenance of normal cell differentiation,

		enhancement of apoptosis, and prevention of tumor angiogenesis[20].
Melatonin	20mg p.o. capsule at h.s	Multi-disciplinary anti-cancer action, reduces toxicity after chemotherapy, radiotherapy, immuno-hormonal therapy and cancer surgery. Adjuvant therapy for cancer[21]. Immunomodulatory in the immunocompromised state[22].

A CT scan (chest, abdomen, pelvis) from September 24, 2012 showed several prominent mediastinal and hilar lymph nodes, unchanged from prior exam (Figure. 2).

Fig 2. CT of the chest, abdomen and pelvis – sagittal – September 2012



LRHT over the chest and abdomen alongside IVAA (50 gms) was initiated on October 9, 2012. DM received 18 and 15 treatments over the lungs and abdomen respectively, completing his cycle on November 17th 2012. He received 3 treatments of FR-WBHT over the six-week treatment protocol, given in weeks 2, 4 and 6. DM

tolerated his treatments well with no reported side effects, and noted a gradual and significant improvement to his quality of life. His symptoms of anorexia, cough, nausea, abdominal pain and discomfort, diarrhea and general weakness all improved during the course of this treatment. Following the 6-week treatment protocol, a CT scan (chest, abdomen, pelvis) from November 15, 2012 found no remaining evidence of pulmonary nodules or chest wall lymphadenopathy (Fig. 3, 4).

Figure 3. CT of the chest, abdomen & pelvis – coronal – November 2012

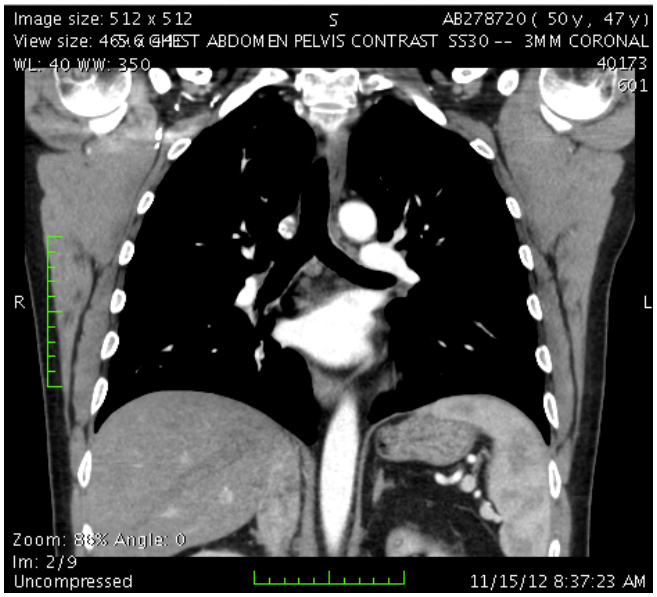
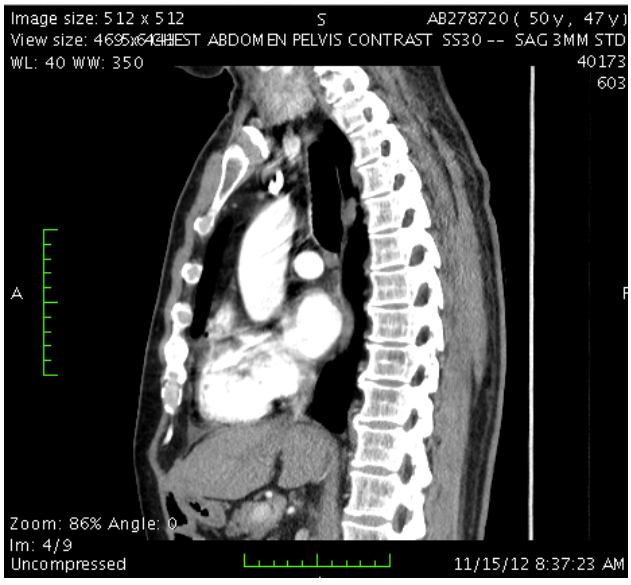
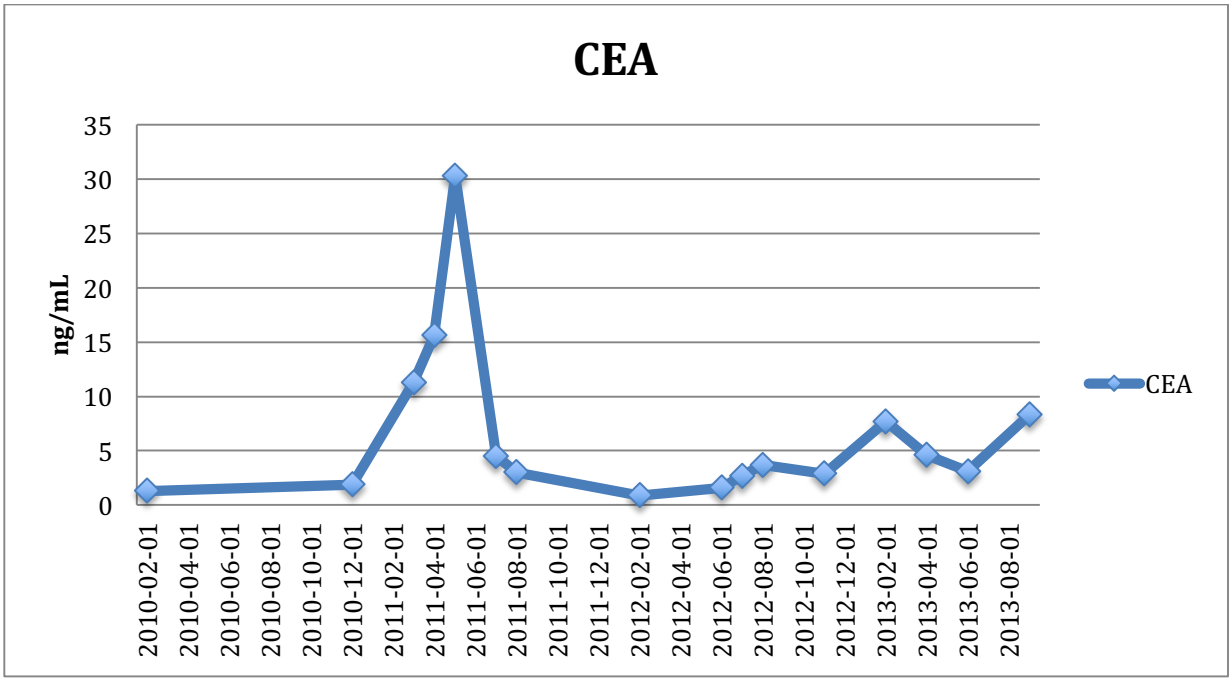


Figure 4. CT scan of chest, abdomen & pelvis – sagittal – November 2012



DM remained stable with a good quality of life. In June 2013, CT of the chest, abdomen and pelvis reported definite improvements in periaortic adenopathy and residual nodes were no longer of pathological size. The previously documented areas of concern in the liver were no longer visible. Lung nodules had also decreased in size from a scan done in February 2013. Carcinoembryonic antigen (CEA) was monitored and showed an improvement in clinical treatment course. (Fig. 5).

Figure 5. – Recorded CEA Values



DM completed his treatment plan November 17th 2012 and clinical remission as evidenced on the CT scan from June 4, 2013. On follow up consultations, he remained asymptomatic. DM subsequently returned to his home and after his follow up CT scan on September 2013, where a solitary lymph node was found in his abdomen, he was recommended to resume chemotherapy. His most recent CT scan from December 2013 did show clinical progression, with lesions noted in his lungs and liver. DM resumed chemotherapy and upon starting conventional treatments was eventually lost to follow-up.

Discussion:

Neoadjuvant chemoradiotherapy may not affect local control and overall survival in locally advanced rectal cancer with distant metastasis[23]. Peritoneal carcinomatosis

occurs in patients with advanced gastrointestinal and gynecological malignancies and also in patients who experience recurrence after treatment failure of the primary tumour. Systemic chemotherapy alone will not be adequate to palliate or treat patients with peritoneal carcinomatosis[24]. The addition of hyperthermia to a patient's treatment regimen, as in this case for example, shows a potential benefit. Both LRHT and FR-WBHT were administered in conjunction with naturopathic treatments. When cancer cells are subjected to high temperatures (40-43° C) they are susceptible to irreversible damage, in a time and dose dependent way[25]. Recent developments based on the thermo-radiobiological rationale of hyperthermia indicate it to be a potent radio- and chemo-sensitizer. This has been further corroborated through positive clinical outcomes in various tumour sites using thermoradiotherapy or thermoradiochemotherapy approaches. Moreover, being devoid of any additional significant toxicity, hyperthermia has been safely used with low or moderate doses of reirradiation for retreatment of previously treated and recurrent tumors, resulting in significant tumor regression[26]. Cancer cells exhibit differences in their cell morphology, membrane fluidity, and gene expression. Heat increases membrane fluidity and instability of cancer cells, leading to cell death directly, or indirectly through increased delivery of cytostatic chemotherapy agents. Heat shock induces expression of p53, a tumor suppressor transcription factor that is often mutated or decreased in cancer cells. Heat induces secretion of chemokines and cytokines, which draw antigen-presenting cells (APC) into tumors and increase macrophage activity and tumor regression[1]. Hyperthermia increases the visibility of tumor cells to the immune system making it more sensitive to lysis by natural killer (NK), and better recognized by CD8+ T cells, [27]. Whole body hyperthermia is intended to kill tumor cells by raising the body temperature. Studies have shown that when the body temperature reaches 41.8°C, tumor cells undergo apoptosis. In addition, studies have shown that the whole-body thermotherapy improves the immune system by stimulating the production of neutrophils to control tumor growth. The combination of whole body hyperthermia with systemic chemotherapy can boost the effect of chemotherapy drugs and the reversal of the anti-inflammatory response during chemotherapy[28]. In an overview of methods for drug delivery to tumors, research shows that reduction of TIFP (Tumor Interstitial Flow Pressure) was temperature and time dependent. The reduction of TIFP was associated with an increase in perfusion and a sustained reduction of hypoxia, which led to an improvement in antitumoral effects when associated with chemotherapy and radiotherapy[29]. A Clinical study by Hager E.D. et Al. of patients with advanced stage colorectal cancer and liver metastases have been treated with hyperthermia alone or in combination with chemotherapy, and that the results show substantial beneficial effect on overall survival time of patients with liver metastases from colorectal cancer[30].

Conclusion

We presented a case of metastatic colorectal cancer with peritoneal disease. This case report shows that integrative oncology treatment is safe and may be effective for the management of metastatic colorectal cancer. The use of naturopathic treatment played an important role in the patient's life extension, wellness and quality of life. Colorectal carcinoma being an aggressive disease should be managed using all possible resources. LRHT, FR-WBHT, and IVAA in combination with chemotherapy and targeted supplementation have been shown to be effective in the management of metastatic colorectal carcinoma with fewer side effects.

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