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Mini Review Article

Medical & Clinical Research

Recurrent Breast Cancer

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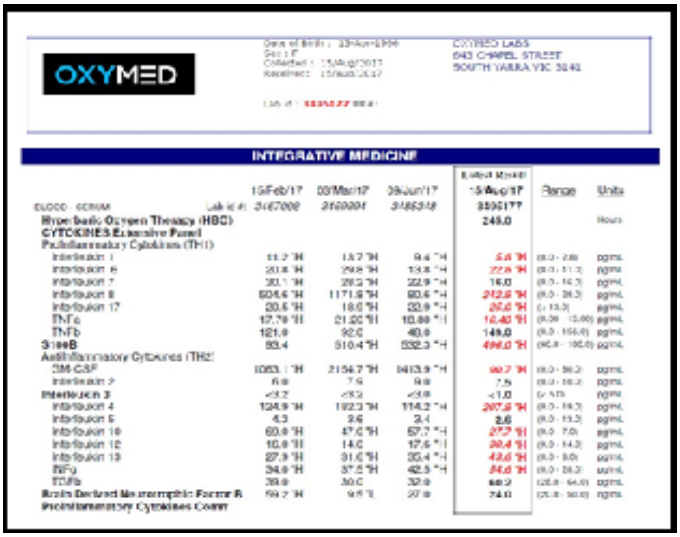
Background information provided by AB

"Previous history of DCIS left breast Nov 2004 - designated Stage 3 with 8(?) Positive lymphnodes. Treatment - Axilla clearance, lumpectomy, 6mo chemo, mastectomy (margins not clear on lumpectomy), radiotherapy, 5 years hormone therapy (Triptorelin and Exemestane - aromatase inhibitors - drug trial .... NO Tamoxifen). Elective right mastectomy and bilateral DIEP reconstruction. Menstrual cycle recommenced after chemo and after hormone therapy. 2016 - Swallowing issues. Ultrasound showed 2 nodules on the right thyroid.

Barium swallow > severe occlusion of oesophagus. Endoscope - initially assessed as a benign fibrotic stricture. Biopsies showed adenocarcinoma - poorely differentiated breast tissue. CT scan - concentric oeophageal tumour of about 4 x 2.5cm and lung right lower lobe mass 1.4 x 1.4cm and right pleural effusion. PET scan - intensely increased uptake oesophagus approx 5cm inferior to carina. Nodal metastasies - multiple active nodes in the mediastinum including right thoracic outlet, right para-tracheal, right tracheobronchial and bilateral hilar regions. There is moderate right pleaural effusion with multiple foci of intense, nodular uptake indicating pleural metastases. These extend into the right costo- diaphragmatic recess adjacent to the lower pole of the right hepatic lobe".


OXYMED

INTEGRATIVE MEDICINE

	15/Feb/17	09/Mar/17	28/Jun/17	15/Aug/17	Range	Units
Hyperbaric Oxygen Therapy (HBO)				248.0		Hours
CYTOKINES Extensive Panel						
Pro-Inflammatory Cytokines (TH1)						
Interleukin 1	11.2 H	13.7 H	9.4 H	5.6 H	(0.0 - 2.8)	pg/mL
Interleukin 6	20.8 H	29.8 H	13.8 H	22.8 H	(0.0 - 11.3)	pg/mL
Interleukin 7	20.1 H	28.3 H	22.9 H	16.0	(0.0 - 16.3)	pg/mL
Interleukin 8	604.6 H	1171.8 H	80.6 H	212.8 H	(0.0 - 26.2)	pg/mL
Interleukin 17	20.6 H	18.6 H	20.9 H	26.0 H	(< 13.3)	pg/mL
TNFα	17.79 H	21.22 H	10.88 H	12.42 H	(0.00 - 13.00)	pg/mL
TNFb	121.0	92.6	40.0	149.0	(0.0 - 155.6)	pg/mL
S100B	93.4	510.4 H	532.3 H	496.0 H	(26.8 - 105.0)	pg/mL
Anti-Inflammatory Cytokines (TH2)						
GM-CSF	1053.1 H	2154.7 H	1413.9 H	99.7 H	(0.0 - 36.2)	pg/mL
Interleukin 2	6.9	7.5	9.9	7.5	(0.0 - 10.2)	pg/mL
Interleukin 3	<3.2	<3.2	<3.0	<1.0	(< 5.0)	pg/mL
Interleukin 4	124.9 H	192.3 H	114.2 H	207.8 H	(0.0 - 19.3)	pg/mL
Interleukin 5	4.3	3.6	2.4	2.6	(0.0 - 13.2)	pg/mL
Interleukin 10	60.8 H	87.6 H	67.7 H	27.7 H	(0.0 - 7.0)	pg/mL
Interleukin 12	10.8 H	14.0	17.6 H	30.4 H	(0.0 - 14.2)	pg/mL
Interleukin 13	27.9 H	31.6 H	35.4 H	43.6 H	(0.0 - 9.0)	pg/mL
INFg	34.8 H	37.5 H	42.5 H	84.6 H	(0.0 - 28.2)	pg/mL
TGFb	39.8	30.0	32.9	88.9	(25.8 - 64.0)	pg/mL
Brain Derived Neurotrophic Factor R	59.2 H	95.1	97.9	74.0	(25.8 - 50.0)	pg/mL
Pro-Inflammatory Cytokines Comm						

Cytokine Interval Testing

Cytokine are gene signal proteins and glycoproteins that 'orchestrate' proper immune responses including inflammation and anti-inflammatory pathways. Cytokines act as mediators and modulators and regulate immunological responses, hematopoietic development, and cell-to-cell communication as well as host responses to infectious agents and inflammatory stimuli. Cytokines are pleiotropic which refers to their ability to address multiple targets and physiological effects [1]. Cytokine production is tightly regulated; their homeostatic concentration in body fluids is low. However, if required, the concentration of cytokines can increase up to 1,000-fold [1]. In healthy individuals, cytokines are either not detectable or present at small concentrations in body fluid or tissues. Elevated concentrations of cytokines indicate activation of cytokine pathways associated with inflammation or disease progression. Metastatic breast cancer prognosis is highly variable, cytokine measurements can assist to better understand the disease progression and monitor the effects of treatment [1-16].

Focus of this case include IL-1, IL-6, IL-8, and S100B.

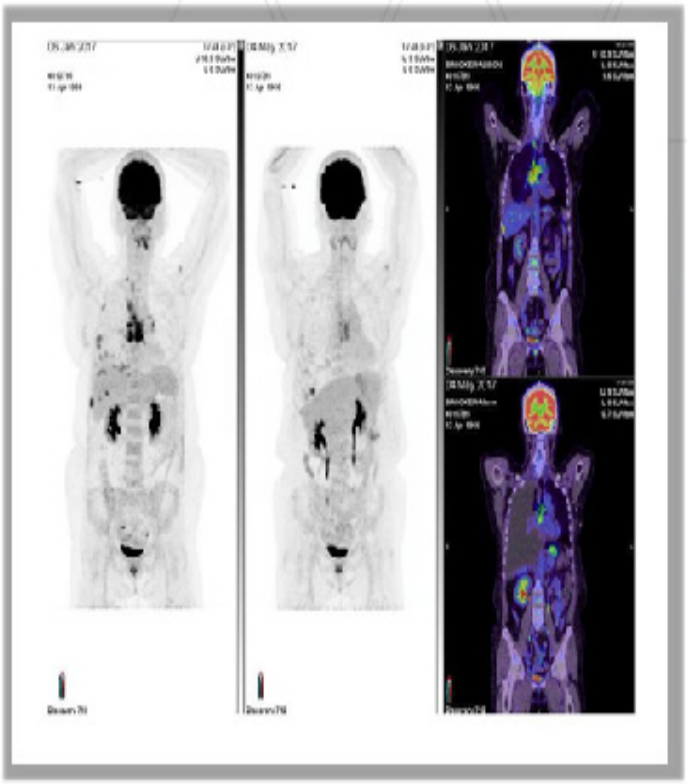
Interleukin 1: (IL-1) with IL-6 and TNFα contribute to acute Cytokine Storm associated with COVID19 comorbidities [3]. IL-1 is linked with systemic inflammation including 'gut and brain connection'. IL-1 is linked with a reduction in the cerebral blood flow and increase in infarct volume [2]. Blockade of endothelin-1 receptors reversed this hypo perfusion, reduced tissue damage, and improved functional outcome. IL-1 is linked in aggressive carcinoma progression including head and neck cancer, pancreatic cancer, thyroid cancer and bladder cancer [5].

Interleukin 6: (IL-6) can increase up to a 1,000-fold during trauma and acute infection and is a major driver of COVID19 mortality [3]. IL-6 is linked with pathological pain associated with bone cancer, peripheral nerve injury, spinal cord injury, chemotherapy-induced peripheral neuropathy [7]. IL-6 is a growth and survival factor in human glioblastoma cells and plays an important role in malignant progression [5].

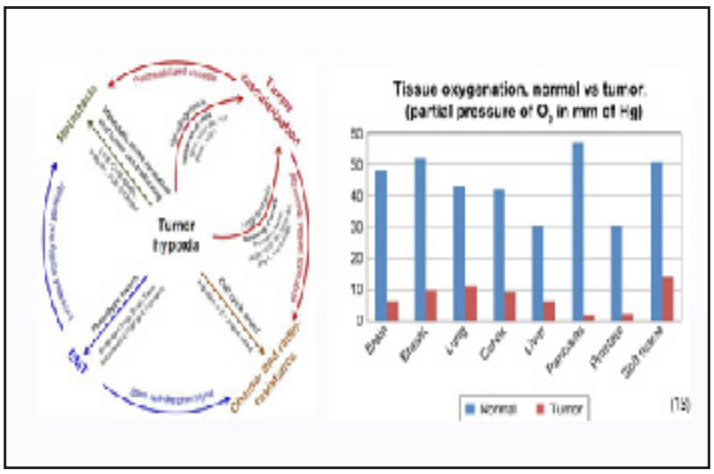
Interleukin 8: (IL-8) is linked with atherosclerosis and cerebrovascular disorders due to the micro-damage of the endothelial vascular wall [12]. Hypoxia increased the release of IL8, which contributes to the aggressive spread of cancer cells [14]. Increased expression of IL-8 and/or its receptors has been characterized in cancer cells, endothelial cells, infiltrating neutrophils, and tumor-associated macrophages, suggesting that IL-8 may function as a

significant regulatory factor within the tumor microenvironment. IL-8 expression correlates with the angiogenesis, tumorigenicity, and metastasis of tumors. Therefore, inhibiting the effects of IL-8 signaling may be a significant therapeutic intervention in targeting the tumor microenvironment [15]. Telomerase activity is required for both initiation and maintenance of tumorigenesis and over 90% cancers overexpress telomerase. IL-8 is a biomarker that predict telomerase inhibition mediated growth attenuation of cancer cells and its loss phenocopy telomerase inhibition. Therefore, IL-8 expression can be utilized as a biomarker for telomerase targeted cancer therapies to potentially predict therapeutic response [16]. IL-6 and IL-8 play important roles in the progression of triple-negative breast cancer (TNBC) and pancreatic ductal adenocarcinoma (PDAC) [16].

S100B calcium-binding protein family are inflammatory molecules that contribute to the development of a pro-inflammatory tumor microenvironment. S100B serves as a marker for metastasis in lung cancer, ovarian cancer and melanoma [17]. However, the association between S100B and the metastasis of breast cancer is not yet well understood. A high S100B expression predicted a good overall survival in patients with ER-negative breast cancer, and good distant metastases-free survival in all patients with breast cancer. A high S100B expression is associated with a good prognosis in patients with p53 mutant and p53 wild-type breast cancers. Our findings demonstrate that S100B treatment suppresses the migratory capacity of ER-negative breast cancer and that S100B expression may serve a predictive marker for metastasis in breast cancer [17].



PET SCAN COMPARISION – INTERVAL 4 MONTHS



Hyperbaric Oxygen Therapy

HBOT is the application of two variables - increased pressure and increased oxygen. Hypoxia is a common feature of malignant tumors. Hypoxia exists to some degree in most solid tumors due to inadequate oxygen delivery of the abnormal vasculature, which cannot meet the demands of the rapidly proliferating cancer cells. The levels of oxygenation within the same tumor are highly variable from one area to another and can change over time [16-20]. There is an interactive connection between hypoxia and chemoresistance, radio resistance, invasiveness, and angiogenesis. Therefore, tumor hypoxia has been considered as a validated target for treating cancer. Hypoxia causes chemoresistance and radioresistance. HBOT is a hypoxia-targeted therapy [18].

The National Cancer Institute describes the mechanism of HBOT. Hyperbaric oxygen may increase the amount of oxygen in cancer cells, which may make them easier to kill with radiation therapy and chemotherapy. It is a type of radio sensitizing agent and a type of chemo sensitizing agent [19]. HBOT assists immune responses to chemotherapy reducing immunosuppression and neutropenia.

HBOT increases the plasma saturation of oxygen. Normal plasma oxygen by volume is 3% (0.3 ml O2/100 mlblood); under HBOT conditions the O2, saturation increases 10-20 times that of breathing room air at normal atmospheric pressure [29]. HBOT has profound effects on immune modulation in the presence of hypoxia. Hypoxia targeting might be relevant to overcome hypoxia-associated resistance in cancer treatment [20]. HBOT may improve the sensitivity of radio-chemotherapy by increasing oxygen tension within the hypoxic regions of the neoplastic tissue [21]. Clinical trials and suggest that radiotherapy immediately after HBOT enhances the effects of radiotherapy in some cases [22-24]. HBOT can strengthen the anti-tumor effect of chemotherapy when applied together [23]. Overall, HBOT is well tolerated and does not significantly increase toxicity [24]. The reoxygenation brings additional benefit of making hypoxic cancer cells even more responsive to the killing effect of a cytotoxin [23].

Discussion

HBOT has been described as the 'integrative bridge' between orthodox medicine and complimentary approaches. Oxygen is essential to drug delivery [25-29]. HBOT significantly suppressed tumor growth in both the triple positive and negative breast tumors.

HBOT significantly reduced both numbers and total area of the metastatic lesions [21]. HBOT reduces inflammatory cytokines including IL-1β, IL-6, IL-8, TNF-α, S100B through several transcription factors regulating inflammation, including hypoxia inducible factor 1 (HIF-1), Nrf2 and NFkB [22, 25]. HBOT has been shown to increase the counter-inflammatory IL4, IL10 and IL13 levels [25]. HBOT upregulates the patients targeted Stem Cells {an 8-fold (800%) increase in circulating CD34+} [27, 28]. HBOT enhances mitochondrial respiration and function [25].

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