Morphologic comparison of three cases of Low Grade Invasive Ductal Carcinoma: one case of 60 y.o. female on phytochemical NRF2 activator for 7 months, one case of 69 y.o. female on neo-adjuvant hormonal therapy for 8 month, one case of 70 y.o. female with no pre-surgical intervention.

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Abstract:

Oxidative stress plays an important role in etiology of breast cancer. Nrf2 is a transcription factor that regulates the expression of a large number of antioxidant and cytoprotective genes; it has been demonstrated to be protective against cancer. Protandim, a proprietary blend of 5 botanicals (bacopa, ashwaghanda, milk thistle, green tea and turmeric), synergistically activates NRF2 factor.

To date, there are no reports on pathologic evaluation of breast carcinoma in patients taking Protandim. We present three cases of breast Invasive Ductal Carcinoma with similar pathologic grade and stage from one patient on Protandim, one patient post neo-adjuvant hormonal therapy and control case of Breast Carcinoma with no previous tumor alteration. The morphologic appearance of breast carcinoma from patient, obtaining Protandim and from patient on Letrozole is quite similar dysplaying cellular degeneration. There is no cellular degenerative effect, identified in control case.

We hypothesized that Protandim, via NRF2 up-regulation, caused tumor cell degeneration.

This is a purely observational study with very narrow “cohort” to draw any conclusions, and further clinicopathologic correlation with more and more similar studies is needed.

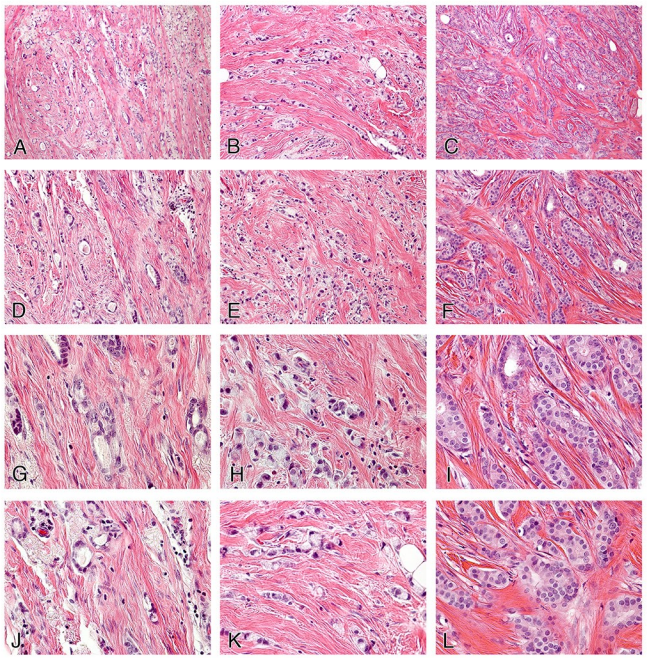
Introduction:

Based on 2009 Canadian Cancer Society estimates:
2 out of 5 Canadians (45% of men and 41% of women) are expected to develop cancer during their lifetimes. 1 out of 4 Canadians (29% of men and 24% of women) is expected to die from cancer. Breast cancer is the most commonly diagnosed cancer in women with 75-80% being estrogen receptor positive. Alterations in the redox balance are involved in the origin, promotion and progression of cancer. Oxidative stress plays an important role in etiology of breast cancer. One of the most important estrogen-related carcinogenic mechanisms is oxidative metabolism of estrogen and subsequent formation of ROS[12]
Nrf2 is a transcription factor that regulates the expression of a large number of antioxidant and cytoprotective genes; it has been demonstrated to be protective against cancer. There is an intricate balance and very complicated relationship between NRF2, estrogen, estrogen receptors and BRCA I gene.

Protandim, a proprietary blend of 5 botanicals (bacopa, ashwaghanda, milk thistle, green tea and turmeric) is proven to activate NRF2 factor in synergistic manner. However, there are no studies or case reports in terms of pathologic evaluation of invasive breast carcinoma in patients, obtaining this NRF2 activator for a period of time.

Methods:

Three cases of invasive ductal carcinoma of breast were identified from my practice and all of them had invasive ductal carcinoma with similar characteristics of low to intermediate grade, based on low to intermediate nuclear grade, low to intermediate architectural grade and low mitotic score, with similar tumor size. Prior to definitive surgery, one patient was on Protandim for 7 month, one patient received a course of neo-adjuvant hormonal therapy with Letrozole (non-steroidal aromatase inhibitor) and one patient had no medical intervention. H&E sections were compared.



Legend:

A. Invasive Ductal Carcinoma, (IDC), H&E X 10, patient on Letrozole neoadjuvant therapy.
B. Invasive Ductal Carcinoma, (IDC), H&E X 10, patient on NRF2 activator (Protandim) for 7 month prior surgical resection.
C. Invasive Ductal Carcinoma, (IDC), H&E X 10, patient with no intervention prior surgery.

D. Invasive Ductal Carcinoma, (IDC), H&E X 20, patient on Letrozole neoadjuvant therapy
E. Invasive Ductal Carcinoma, (IDC), H&E X 20, patient on NRF2 activator (Protandim) for 7 month prior surgical resection.
F. Invasive Ductal Carcinoma, (IDC), H&E X 20, patient with no intervention prior surgery.

G. and J. Invasive Ductal Carcinoma, (IDC), H&E X 40, patient on Letrozole neoadjuvant therapy.
H and K. Invasive Ductal Carcinoma, (IDC), H&E X 40, patient on NRF2 activator (Protandim) for 7 month prior surgical resection.
I and L. Invasive Ductal Carcinoma, (IDC), H&E X 40, patient with no intervention prior surgery.

Results:

It was observed that tumor in a patient on Protandim and tumor in a patient on Letrozole had similar morphologic appearance in terms or ductal elements and stromal component. Degenerative effect was observed in neoplastic cells and stroma showing cytoplasmic bluish discoloration, either “washed” or very dense chromatin. The invasive ductal carcinoma from the patient with no prior therapy or no supplement intake shows vibrant nuclear features with powdery chromatin and eosinophilic cytoplasm. The stroma is also eosinophilic with abundant myofibroblasts.

Discussion:

Recent reports show that NRF2 expression was decreased in certain human breast cancer cells and breast tumors when compared with normal mammary epithelial cell or normal breast tissue. It was shown that NRF2-mediated induction of the cellular antioxidant response is an efficient strategy to tackle in vivo tumor growth in transformed adult stem cells. NRF2 sensitizes transformed cells to apoptosis. Also the presence of antioxidants is found to improve the cytotoxic effect of apoptosis-inducing agents[1].

It was speculated that Protandim, an NRF2 activator and a proprietary blend of 5 botanicals (bacopa, ashwaghanda, milk thistle, green tea and turmeric) might have caused the neoplastic cells degeneration. The nature of this cellular degeneration is not clear and it may be related to up-regulation of multiple nuclear/molecular pathways, whether it is an up-regulation of multiple antioxidant enzymes, such as glutathione S-transferases, thiioredoxin, thioredoxin reductases, peroxiredoxins, y-glutamyl cysteine ligase, heme oxygenase 1, NADPH, SOD, or down-regulation of epithelial-mesenchymal transition[6].

This is a purely observational study with very narrow “cohort” to draw any conclusions, and further clinicopathologic correlation with more and more similar studies is needed.

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