

Anorexia in Cancer Cases: A Critical Review of the Causes and Mechanisms

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Abstract

Anorexia is one of the most prevalent clinical presentations seen associated with cancer. It is also one of the most difficult clinical presentations experienced by cancer patients during and after treatment. It is known that both the disease and its management may affect the triad of taste, smell and appetite for prolonged periods leading in many instances to malnutrition and cachexia. Anorexia is thus a cause of social concern the world over. The causes of anorexia in cancer are multiple. It can be due to defect in either central or peripheral mechanism for appetite or even due to toxicity of drugs consumed for cancer. Centrally it can occur due to depression and agonizing pain resulting in alteration of hypothalamic neurotransmitters that modulates feeding. Peripherally anorexia can be due to pro inflammatory cytokines, lactate, tryptophan etc. The anorectic effect of chemotherapy also alters the perception of taste.

Key words

Cancer, anorexia, neurotransmitter, cytokines.

INTRODUCTION

Anorexia is a persistent loss of appetite resulting in less intake of food, gradually leading to the depletion of body weight resulting in Anorexia – Cachexia Syndrome. The peripheral cause of cancer allied anorexia is either pro inflammatory cytokines or increase in lactate¹ which directly controls the neurotransmitter signaling resulting in the dysfunction of hypothalamus signaling mechanisms. Recent evidence indicates that homeostatic control of energy, i.e. regulation of food intake and expenditure, is mediated within hypothalamus and inflammatory cytokines contributes to the development of anorexia associated with cancer².

During tumor growth, the patient's immune system may trigger the inflammatory response of the body which is primarily mediated by cytokines (i.e. tumor necrosis factor (TNF α), Interleukin IL-1, IL-6, etc.). Scanning of the available research data on the studies in anorexia nervosa unveils the pivotal role of the immune system in its pathophysiology. Specifically, this data shifts focuses between the increased levels of various pro-inflammatory cytokines on one hand and the spontaneous production of tumor necrosis factor on the other. Genetic studies further support a dysregulated immune system in anorexia³.

The primary aim of this study is to summarize the multiple causes of anorexia and to table the mechanism of central and peripheral causes of anorexia, based on a battery of studies related to anorexia in cancer. This study also examines the concept of aruchy mentioned in Ayurveda with reference to the key factor of health and illness, agni.

CAUSE AND MECHANISM OF ANOREXIA

Appetite and eating are regulated by a multitude of gastrointestinal, physiological, metabolic, and nutritional factors, as well as neuronal and endocrine mechanisms. In the cancer patient, anorexia may be due to both disease and treatment related factors. Some factors may be related to stress also. Gastrointestinal changes, alteration in metabolic activities, cytokine activity, psychological issues are the factors leading to anorexia in cancer⁴.

Hypothalamus is the principal area in the brain involved in the regulation of appetite. Gut is influenced profoundly by hypothalamus in the hunger and satiety see-saw. It is known that activation of serotonergic system at ventro-medial hypothalamus (VMH) triggers the feeling of satiation, thereby reducing hunger.

Central causes of anorexia can be depression, pain, or alteration in central neurotransmitters. Patients diagnosed with cancer have the tendency to develop acute anxiety related to curability and survival; leave alone the social and financial burdens and stigmas they have to shoulder as part of therapy. The fear of pain may affect daily activities; gradually the sufferers may fall into a state of depression. Changes in their neuro-endocrine axis finally leads to anorexia.

Imbalance in the neurotransmitters

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like serotonin and Corticotropin- Releasing Factor (CRF) cause depression and this engender anorexia⁵⁻⁶. It has also been reported that when cancer patients are infused with interferon, there is an increased production of kynurenine (KYN), the pathway of which is associated with depression and anorexia⁷. This leads to alterations in tryptophan and serotonin levels and stimulate Corticotrophin-Releasing Factor.

Cytokines

Cytokines are group of peptide hormones released by lymphocytes and monocyte macrophages, released into the blood from immune cells affected by the immunotherapy such as monoclonal antibodies and CAR-T cells. They may be released into the circulation and transported to the brain through the BBB (Blood-Brain-Barrier) and circum-ventricular organs. Their sudden release – cytokine storm, also called hypercytokinemia – is associated with a host of manifestations from mild symptoms like fever, nausea, headache, rash, tachycardia, hypotension and dyspnea to life threatening presentations. They interact with the luminal surface of brain endothelial cells causing release of substances that affect appetite⁸. Inflammatory cytokines such as Tumor Necrosis Factor alpha (TNF α), Interleukin-1 (IL-1), and Interleukin-6 (IL-6) are elevated in many cancers⁹⁻¹⁰.

a. Tumor Necrosis Factor-Alpha (TNF α)

It is known that TNF α – induces weight loss in malignancies and chronic infections. Whereas short-term caloric deprivation stimulates TNF-alpha production in in-vitro models, spontaneous production of TNF-alpha in increased quantities has been found in cases of anorexia nervosa. It is debatable whether the role of TNF –alpha is the cause or effect in anorexia¹¹. However, it has been observed that chronic undernutrition is not always associated with increased TNF-alpha production. At the same time, experimental use of naloxone, a TNF α down-regulator in the treatment of anorexia nervosa was found successful and is supposed to act by inhibiting TNF production which reactivates lipid synthesis and reverses insulin resistance¹².

b. Interleukin-1

This is produced by lymphocytes and macrophages and helps in reducing the size, duration and frequency of meals without reducing the desire for food¹³. It acts directly by crossing the blood-brain barrier or by activating ascending fibers of vagus¹⁴. IL-1 enhances serotonin activation and stimulates CRF production in the hypothalamus leading to anorexia¹⁵. Antibodies to IL-1 is known to enhance food intake in tumor-bearing rodents¹⁶. During the growth of the tumor, IL-1 is produced or secreted in excess, which in turn helps supply tryptophan to the brain. In VHM, receptors to IL-1 exist, which releases serotonin. In short, while centrally acting IL-1 increases serotonin release in the brain by augmenting hypothalamic neuronal firing rate; peripherally acting IL-1 supplies hypothalamus with tryptophan, its precursor to maintain consistently high serotonin synthesis.

c. Interleukin -6

Interleukin – 6 (IL-6) being a pleiotropic cytokine, has numerous actions like immune function, hematopoiesis, metabolism and oncogenesis¹⁷. This is secreted by T-cells and macrophages, microglia, astrocytes and neurons. Its action in inflammation is dual and enigmatic: pro-inflammatory and anti-inflammatory, condition wise dependent. IL-6 regulates progression of cancer and cancer associated cachexia through both direct and indirect targeting of multiple systems, altering metabolism and endocrine function¹⁸. It has specific role in cachexia of colon-26 adenocarcinoma bearing mice. Its direct role in cancer anorexia is yet to be founded.

Leptin

It is an adipokine (adipocytokines) produced from fat tissues, producing anorexia within the Central Nervous System. Serum leptin levels are low in untreated anorexia nervosa. It reduces subcutaneous fat and increases physical activity, perhaps by inhibiting the release of NPY (Neuropeptide Y, a 36 amino acid neuropeptide) by hypothalamus¹⁹, causing anorexia.

Lactate

Lactate is a potent anorectic agent, which reduce food intake. Experimental studies have demonstrated that both intravenous and intraportal infusion of lactate inhibits spontaneous food intake in rats²⁰.

When tumor activates the production of lactate, it will be transported across the blood brain barrier by monocarboxylate transporters (MCT), thereby interfering the glycol-sensing mechanism in the hypothalamus. Lactate suppress food intake by activating adenosine monophosphate (AMP) methyl malonyl CoA signaling pathway²¹. It also activates the ventro-medial hypothalamus and dorso-medial hypothalamus without any alteration in CRF.

Dopamine and Serotonin

Activity within the hypothalamus is mediated by two neurotransmitters: Dopamine and serotonin. These helps initiation, maintenance and then inhibition of eating. At the onset of eating dopamine activity increases in the lateral hypothalamus and mesolimbic

dopamine system. As eating continuous dopaminergic activity is phase-wise replaced by serotonergic activity; which reduce appetite and inhibits eating. In anorexia, because of the extreme low level of dopamine, patient seldom experience pleasure or reward. Increase of serotonin levels lead to satiety and lesser food consumption. Lower serotonin levels on the contrary results in excessive eating and obesity. Dieting reduces tryptophan (precursor of serotonin) levels which stimulate CRF and leads to anorexia.

Gastro Inhibitory Polypeptide

Gastro inhibitory peptide (GIP), a recently identified gastrointestinal polypeptide, has known glucose- dependent insulinotropic action. It has also inhibitory effect on gastric motility and secretions. A number of GIP such as cholecystokinin, amylin etc. have been demonstrated to be anorectic.

Ayurvedic Considerations of Cancer Associated Anorexia

Aruchi is recognized as a separate disease and also considered as a potentially fatal medical condition. And it is one of the major symptoms manifested during acute and chronic pathophysiological process including malignancy. Aruchi is one among the tridoshaja vyadhi and is classified according to doshas and manasika factors like chinta, bhaya, shoka, krodha etc. Along with the impaired dosha and manasika factors digestive fire become depleted and leads to agnimandhya. To treat agnimandhya ingredients of katu – tikta rasa along with laghu ruksha and tikshna guna pradha dravyas are more beneficial.

In cancer patients the digestive fire is so overcast owing to the manasika factors and the cocktail treatment agents and gradually develop aruchi, one of the leading comorbidities.

Agni is pivotal in all biological functions²². It is instrumental in almost all endogenous diseases either directly (as in jvara²³) or as an undercurrent (as in rajayakshma²⁴). Its sluggishness is the important factor in almost all dhatuparinama janya roga²⁵. When agni is sub-optimal, anorexia is a common presentation, as ruci is the physiological manifestation of optimal function of agni. Its reduction is met with in a spectrum of diseases like arsa, atisara, grahani etc., to name a few²⁶. In majority of debilitating diseases like rajayakshma, ruci is lost – aruchi is one of the ekadasa roopam of this condition too²⁷. This fact can be surrogated to cancer also, as there are many factors analogous in both cancers and rajayakshma. Moreover, if the general belief that rajayakshma can be related to tuberculosis only is shed; one can find many an identity between cancers and rajayakshma including ojakshaya. In another words, management of aruchi happens to be one of the chief objectives of cancer therapy. This is possible only if agni is made optimal.

Conclusion

The central nervous system and particular areas in hypothalamus play crucial role in the pathogenesis of cancer allied anorexia. The role of pro-inflammatory cytokines as well as of neuro-transmitters in anorexia are determinants of compromised immune system in cancer patients. The exact mechanism of anorexia is complex. From

ayurvedic perspective it can be stated that agni is affected in cancer cases, which leads to aruchi and arathi, further leading to diminished ojus. Protection of agni is hence the principal therapeutic strategy to be considered in the management of cancers and cancer allied anorexia.

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