Nutritional Support in Cancer

Module 26.2

Cancer Anorexia

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Learning Objectives

- Understand the clinical relevance of cancer anorexia;
- Understand the pros and cons of the available tools for the diagnosis of cancer anorexia;
- Understand the pathogenic mechanisms of cancer anorexia;
- Understand the role of the central nervous system in controlling host metabolism during tumour growth.

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Key Messages

- Cancer anorexia is clinically relevant since it is an independent negative prognostic factor and contributes to worsen quality of life;
- The presence of cancer anorexia should be qualitatively and quantitatively assessed;
- Tumour-induced neuro-inflammation contributes in a major way to the pathogenesis of cancer anorexia;
- Cancer-associated anorexia and tissue wasting may share common pathogenic pathways involving brain areas controlling energy homeostasis.

1. Introduction

Malignancy, but also other chronic diseases, including chronic obstructive pulmonary disease (COPD) and end-stage renal insufficiency, is characterized by the progressive deterioration of nutritional status, leading to worsened clinical outcome (1). Consistent evidence indicates that this syndrome is the clinical manifestation of the moderate, persistent and systemic inflammatory response induced by the underlying disease. The main factors contributing to severe malnutrition during disease are the development of anorexia, i.e., reduced appetite and energy intake, and profound metabolic changes occurring in peripheral tissues, including increased muscle proteolysis, usually referred as cachexia (1). Therefore, during the last decades, the characteristic nutritional deterioration occurring during disease has been defined as the anorexia-cachexia syndrome. The better knowledge of the mechanisms of anorexia and tissue wasting now suggests that they may share a number of pathogenic pathways, particularly those involving the activity of specialized hypothalamic areas modulating energy homeostasis. Consequently, the term cancer cachexia is now becoming more frequently used in the clinical setting to define the progressive deterioration of nutritional status of cancer patients, irrespective of the relative contribution of anorexia and metabolic changes.

2. Cancer anorexia

The cachexia syndrome can be defined as an inflammation-driven physiological response to external and/or internal insults. The behavioural and metabolic modifications elicited by acute diseases or trauma are supposed to help the organism to heal and recover. However, in the presence of a chronic disease, including cancer, the cachexia syndrome becomes detrimental since its persistent impact on energy intake and host metabolism depletes protein and energy stores, increases the risk of complications and eventually accelerates death.

One of the main features of the cachexia syndrome is the development of reduced food intake, i.e. anorexia. The clinical relevance of anorexia is underscored by its significant association with increased risk of death in hospitalized patients (2), and particularly in cancer patients (3). Also, anorexia impinges on quality of life. Ravasco et al. demonstrated that the reduction of food intake is a key factor in determining cancer patients' quality of life (4).

2.1. Prevalence and severity

Anorexia and reduced food intake are frequently encountered in cancer patients (5). DeWys et al., in their classical paper, showed that approximately 50% of cancer patients report abnormalities of eating behaviour even at the time of diagnosis (6). In terminally ill cancer patients, the prevalence of anorexia is approximately 60% (7), but it should be acknowledged that in this clinical setting, anorexia may also result from previous therapeutic treatments. Until now, little attention has been paid on the possible similarities between the pathogenic pathways of anorexia and tissue wasting, prompting the assumption that anorexia and wasting could be present only incidentally in the same patient. Increasing evidence now challenges this view, and suggests that anorexia and metabolic changes could represent different manifestations of the same neurochemical/metabolic derangements.

2.2. Diagnostic tools

Difficulties still exist in clearly defining and diagnosing anorexia (8). A visual analogue scale is sometimes used. More often the diagnosis of anorexia is based on the presence of reduced energy intake. A simpler approach is based on the use of questionnaires (e.g., the North Central Cancer Treatment Group questionnaire, and the Functional Assessment

of Anorexia Cachexia Therapy, FAACT, questionnaire), or on the identification of symptoms interfering with food intake and likely to be related to changes in the central nervous system control of energy intake (8). However, all these tools present disadvantages, including the difficulty to provide a qualitative and quantitative assessment of the presence of cancer anorexia. To this end, the European Society for Clinical Nutrition and Metabolism (ESPEN) has recently developed an Anorexia Questionnaire, adapted from AC/S-12 of FAACT questionnaire (9). This diagnostic tool includes 12 questions related to appetite and eating behaviour, whose multiple answers are anchored to a score. A total score ≤24 has been proposed as being sufficient to make diagnosis of anorexia (9).

3. Pathogenesis of cancer anorexia

Under physiological conditions, energy intake and body weight are modulated by the hypothalamus. The hypothalamus integrates neural, metabolic and hormonal signals originating from peripheral tissues, which convey information about energy store status (10). More specifically, the arcuate nucleus of the hypothalamus (the infundibular nucleus in humans) contains specific neuronal populations transducing these inputs into neuronal responses and, via second order neuronal signalling pathways, into behavioural and metabolic responses (10). Intuitively, cancer associated anorexia might result from defective peripheral signals, from an error in the transduction process, or from deranged activity of the second order neuronal signalling pathways.

3.1. The melanocortin system

Two different subsets of neurons with a key role in the homeostasis of food intake and energy expenditure are colocalized in the hypothalamic arcuate nucleus. The first population of neurons expresses pro-opiomelanocortin (POMC)(10). POMC has no biological activity, but is cleaved into smaller biologically active peptides, the melanocortins, the most important being the α -melanocyte stimulating hormone (MSH) (10). The biological effects of melanocortins are mediated by specific receptors (11), the melanocortin-4-receptor (MC4R) having a critical influence on the regulation of energy balance by mediating anorectic and catabolic responses.

The second population of neurons expresses neuropeptide Y (NPY) and agouti-related protein (AgRP). Interestingly, AgRP is the endogenous antagonist of MC4R thereby antagonizing the effect of α-MSH (10). This evidence shows the reciprocal relationship between the two neuronal subsets. Both populations project to other second order hypothalamic nuclei.

In the presence of excess energy, POMC neurons are activated and trigger the release of melanocortins that in turn activate MC4R, leading to suppression of food intake and increase in energy expenditure. Simultaneously, the activity of arcuate AgRP/NPY is switched off. In contrast, when energy stores are depleted, the activity of anorexigenic POMC neurons is decreased but the activity of orexigenic NPY/AgRP neurons is increased.

Cancer anorexia is characterized by hypothalamic resistance to peripheral signals (12). The hypothalamic resistance to peripheral signals appears to be mediated by the persistent activation of POMC neurons. In experimental models of cancer, MC4R knockout rats resist the reduction of food intake and loss of lean body mass (13). Central infusion of AgRP in cachectic animals ameliorates anorexia and improves body composition (14). This suggests that decreased activity of NPY/AgRP neurons should parallel the hyperactivation of POMC/CART neurons during disease.

3.2. Role of pro-inflammatory cytokines

The role of pro-inflammatory cytokines, and particularly interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α), in the pathogenesis of cancer anorexia has been recognized for many years. In tumour-bearing rats with anorexia, hypothalamic IL-1 mRNA expression is significantly increased (15). Also, IL-1 concentrations in the cerebrospinal fluid of anorectic tumour-bearing rats are increased and inversely correlate with energy intake (16), while intrahypothalamic injection of the IL-1 receptor antagonist ameliorates anorexia in the same experimental model (17).

3.3. Hypothalamic serotonergic activity

The role of serotonin in mediating satiety under physiological condition through its effects in the hypothalamus is well established (18). This prompted studies on its influence in inducing anorexia during catabolic states. In experimental tumour models, anorexia is associated with increased hypothalamic serotonin levels, as assessed by in vivo microdialysis (19), and increased expression of serotonin receptors (20).

In humans, the contributory role of serotonin in cancer anorexia has been inferred by the frequent report of increased plasma and cerebrospinal fluid levels of the amino acid tryptophan, the precursor of serotonin, in cancer patients with anorexia (21). Also, the therapeutic strategy of reducing brain entry of tryptophan has been shown to ameliorate energy intake and nutritional status in cancer patients (22).

Intriguingly, the melanocortin system appears to be involved in the anorectic effects of serotonin (23). Also, the biological effects of serotonin and IL-1 are largely mediated by the same pathways involving the hypothalamic melanocortin system. Peripheral infusion of IL-1 induces anorexia and raises brain tryptophan levels, thereby suggesting increased serotonin synthesis (24). These data indicate that during cancer, increased hypothalamic expression of IL-1 and increased release of serotonin occur.

3.4. Role of the autonomic nervous system

In a classical paper, vagotomy was shown to prevent the development of anorexia in tumour-bearing animals (25) thus suggesting that the vagus might be involved in signalling to the brain about a tumour, and that this signalling is important in the behavioural response (i.e., reduced food intake) to tumours. More recently, it has been demonstrated that the peripherally growing hepatoma induces anorexia and reduced food intake by activation of brainstem neuronal structures, including the nucleus of the solitary tract, an area innervated by the vagus nerve (26).

The mechanism(s) of vagal activation during peripheral challenge remains to be completely elucidated. It has been proposed that proinflammatory cytokines could be involved (27). Direct evidence of the role of autonomic nervous activity on food intake and muscle protein degradation during human diseases is lacking. However, the anabolic effects of ghrelin administration in patients with anorexia-cachexia are paralleled by reduced sympathetic nerve activity (28, 29).

3.5. Role of hypothalamic fatty acid oxidation (energy signals)

Hypothalamic fatty acid metabolism contributes to the modulation of food intake and energy metabolism. Hypothalamic malonyl-coenzyme A (CoA) is a substrate of fatty acid synthase (FAS) and acts like an indicator of global energy status (30). Its concentration is low in the fasted mice and rapidly increases on refeeding (30). Therefore, high intrahypothalamic malonyl-CoA induces anorexia by inhibiting fatty acid oxidation, whereas low levels elicit food intake. The FAS/malonyl-CoA pathway could be involved in

the pathogenesis of cancer anorexia since in vitro studies show that pro-inflammatory cytokines inhibit fatty acid oxidation (31). Furthermore, the orexigenic effects of carnitine in anorectic and cachectic patients could be also related to a presumed carnitine enhancing effect on fatty acid oxidation (32).

4. Cancer anorexia, cancer anorexia-cachexia and cancer cachexia: Different names for the same syndrome?

The well-established role of brain neurochemistry in influencing not only appetite, but the host metabolism in peripheral tissues as well, suggests that anorexia and tissue wasting may share a number of common pathways. Therefore, as previously proposed (12), the pathogenesis of nutritional deterioration during disease could be related to deranged hypothalamic control of energy homeostasis, whereas the different combinations of anorexia and tissue wasting observed in clinical practice may result from the specific interaction of the different genetic profiles of the host and of the growing tumour.

If we assume that the pathogenesis of cancer anorexia and tumour-associated tissue wasting is, at least in part, common, then it may be more appropriate to refer to the constellation of symptoms and signs leading to weight loss using a single term, i.e., cachexia, rather than anorexia-cachexia, which may imply a distinction between anorexia and cachexia. Unfortunately, although easily identified by its clinical characteristics, such as severe weight loss, wasting of muscle and fat mass, anorexia, fatigue, etc., a generally acknowledged definition of cancer cachexia does not exist yet.

A number of proposals have been suggested. In particular, cancer cachexia has been related to increased inflammatory response (as defined by increased C-reactive protein levels), reduced energy intake (<1500 Kcal/day), and weight loss (>10% vs usual body weight)(33). More recently, ESPEN has endorsed the Washington definition which refers to cachexia as a complex metabolic syndrome associated to an underlying illness, and characterized by loss of weight and muscle mass with or without the loss of fat mass (34).

Although any of these definitions allows the identification of cancer patients at risk of poorer outcome, on the other hand, patients meeting the criteria of cancer cachexia are likely to be in an advanced stage of nutritional depletion, which may limit the benefit of nutritional intervention. Therefore, the identification of symptoms related to the early phases of cachexia, or pre-cachexia, may be of more help in identifying the higher risk patients and permitting the prompter start of nutrition therapy. To this end, Bozzetti et al. divided 1307 cancer patients into 4 groups based on combinations of body weight loss (< 10% signifying precachexia; > or = 10% indicating cachexia) and the presence/absence of at least 1 of: anorexia, fatigue, or early satiation (35). Moving from "asymptomatic precachexia" (group 1) to "symptomatic cachexia" (group 4), there were statistically significant trends in the percentage of gastrointestinal vs. nongastrointestinal tumours, severity of cancer stage, percentage of weight loss, number of symptoms per patient, Eastern Cooperative Oncology Group performance status, and nutritional risk score. More recently, ESPEN proposed that pre-cachexia could be diagnosed in the simultaneous presence of underlying chronic disease, unintentional weight loss $\leq$5% of usual body weight during the last 6 months, chronic or recurrent systemic inflammatory response, and anorexia or anorexia-related symptoms (9).

Although extremely useful to categorize a syndrome whose prevalence amply varies according to the diagnostic criteria used, these definitions should be considered as operational and based on experts' consensus. Therefore, they should be validated by prospective studies and prove their consistency within the clinical setting. The Washington definition (34) is based on the presence of weight loss and an underlying disease (i.e., cancer). Although this definition considers other features as complementary criteria for cachexia (e.g. anorexia, anaemia, etc.), weight loss remains the cornerstone

of cancer cachexia (34). Therefore, it could be assumed that in the absence of weight loss, patients cannot be defined as cachectic. Lasheen & Walsh have recently studied the symptoms reported by 484 patients with advanced cancer originating from different organs and particularly from lung, colorectal, breast, pelvic and prostate tumours (36). Twenty-six percent of the patients did not complain of weight loss or anorexia. On the other hand, approximately 1/3 of patients complained of anorexia, 10% reported significant and involuntary weight loss and 31% reported anorexia and weight loss. Therefore, according to the Washington definition, 41% of the cancer population studied met the definition of cancer cachexia. In clinical medicine, any definition and the attendant diagnostic criteria are valuable since they identify patients at higher risk of negative clinical outcomes. Therefore, it could be assumed that the outcome of the cachectic patients (i.e., those with weight loss or weight loss and anorexia) should be different from that of the cancer patients with anorexia but no weight loss. In contrast, the survival of cancer patients with weight loss only, anorexia only, and weight loss and anorexia did not differ (36). These results suggest that cancer cachexia is a multifaceted syndrome in which anorexia and weight loss due to wasting are clinically relevant symptoms, which are not mutually exclusive.

Therefore, it seems that molecular and clinical evidence indicate that cancer cachexia should be better defined as a complex clinical syndrome, which is clinically characterized by a varying combination of anorexia and tissue wasting (37).

5. Summary

The clinical course of cancer patients is frequently characterized by the development of severe malnutrition, which negatively influences morbidity and mortality. Reduced energy intake (i.e., anorexia) and profound changes of host metabolism (usually referred as cachexia) are the main factors leading to the deterioration of nutritional status of cancer patients. Thus, this constellation of signs and symptoms has been termed as anorexia-cachexia syndrome. The pathogenesis of cancer anorexia is multifactorial, but the main feature is the development of insensitivity to peripheral metabolic signals by hypothalamic areas modulating energy homeostasis. This hypothalamic resistance is largely mediated by neuroinflammation. Consistent evidence suggests that the autonomic nervous system could play a major role in mediating the hypothalamic inflammatory response to a peripherally growing tumour. Intriguingly, it appears that most of the cancer-associated metabolic changes in peripheral tissues (e.g. increased energy expenditure, insulin resistance, etc.) could be triggered by efferent autonomic pathways. This evidence suggests that the different clinical features of the anorexia-cachexia syndrome could be related, at least in part, to deranged brain neurochemistry. Therefore, considering that anorexia and tissue wasting share a number of common pathogenic mechanisms, it appears appropriate to define this multifaceted clinical syndrome as cachexia, which now encompasses the different clinical combinations of anorexia and tissue wasting encountered in the clinical practice

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