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Anorexia-cachexia syndrome in a patient with advanced gastric cancer: a case report and review of the literature

Abstract

The aim of this case report is to depict conservative symptomatic treatment in a patient with anorexia-cachexia syndrome and to discuss the possible interventions for such patients. The mechanisms and clinical management of anorexia-cachexia syndrome are discussed. A 79-year-old woman was admitted to hospice-at-home care due to the progression of an inoperable cardia cancer, with symptoms of dysphagia, cachexia and weakness. Due to the advanced stage of the cancer, general poor condition and concomitant disease (Parkinson's disease, diabetes mellitus, myocardial infarction), the patient did not qualify for surgery or chemotherapy. As the patient refused a gastrostomy, she was treated with symptomatic measures (pharmacotherapy) with the important contribution of a surgeon who several times performed endoscopic cardia dilatation, which enabled her feeding through the oral route until death and improved the patient's quality of life. Due to social problems, low food intake, dehydration, electrolyte imbalance and the consideration of parenteral nutrition, the patient was admitted to the inpatient unit, where she died suddenly after five days.

Key words: advanced cancer, cancer anorexia-cachexia syndrome, gastric cancer, management, treatment

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Introduction

Cancer anorexia-cachexia syndrome (CACS) is common in patients with advanced stages of the disease and 55–70% of these patients usually suffer from the symptoms. According to estimations, cachexia is the cause of death in 30% of patients with advanced cancer [1]. Unfortunately, due to common and unspecific symptoms, it is difficult to define CASC precisely. The term "cachexia" derives from Greek: kakos — bad and heksis — state, condition. Cachexia is best defined as a syndrome connected with progressive weight loss, weakness, loss of appetite and metabolic disturbances with impaired function of the immunology system. It is associated with loss of muscle mass, characterized by increased catabolism of skeletal muscle and decreased protein synthesis [2]. CACS is a cytokine-driven dysregulation of the peripheral signals (mainly leptin, ghrelin and serotonin) which play a central role in unbalancing the orexigenic and anorexigenic signals and leads to decreased food intake and an increase

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of resting energy expenditure (primary cachexia). However, when the disease disrupts the integrity of the gastrointestinal tract, development of CACS is called secondary cachexia [3]. The final outcome of CACS is multiple organ failure, water-electrolyte imbalance, anaemia and hormonal dysfunction [4]. From the clinical point of view, quality of life (QOL) deterioration due to weakness and a negative influence on the psychological condition of a patient is one of the important features of the syndrome [5]. The loss of weight may cause changes in body image which negatively influence patients' social functioning. A poor sensation of well-being may also evoke a fear of dying, anger, depression, spiritual pain and the feeling of being a burden to relatives. Cachexia causes the loss of important values, such as work, social activity, avocation and dignity, and in consequence often the development of depression [6]. The aim of this article is to describe what palliative care can achieve for patients with CACS and to discuss the possible interventions in such patients.

Case report

A 79-year-old woman was admitted to a hospice-at-home facility due to an inoperable cardia cancer with anorexia-cachexia syndrome. Her history revealed previous chronic atrophy and pharynx inflammation, myocardial infarction, pneumonia, Parkinson's disease, diabetes type 2 and depression. The first symptoms (weakness, loss of weight, swallowing difficulties and pain in the upper abdomen) dated from nine months before the diagnosis but the endoscopic investigations performed did not show cancer presence. In May 2008 repeated endoscopy and contrast radiography revealed advanced adenocarcinoma of the stomach (G2). Stomach resection was attempted but abandoned due to local infiltration. Due to poor general condition and co-morbidities, she did not qualify for other oncological treatment. She persistently refused the insertion of nutritional gastrostomy, jejunostomy or stenting. In June 2008 she was referred to the local hospice-at-home service. She was treated symptomatically until December 2008. Endoscopic cardia dilatation was repeated bi-monthly, which enabled her to feed orally until the end. On admission to hospice-at-home she had had a weight loss of 20 kg since the first symptoms, and complained of mild to moderate upper abdominal pain (3–4 on a numerical rating scale: 0 — no pain, 10 — the most severe pain), belching after meals, fatigue, lack of energy, lack of appetite, constipation, nausea, hiccups, flatulence, dry mouth, decreased taste of food and dysphagia. She also reported insomnia, difficulties in concentration, irritability, worrying, depressive mood, the lack of an aim in life, anxiety, poor QOL and poor general well-being, and dyspnoea on slight effort. She needed assistance in all her activities and was confined to her flat. On physical examination, her general condition was poor. There was no confusion. A pathological mass in the middle upper abdomen, enlarged liver and a moderate leg oedema were found. Her performance status was ECOG 3–4, Karnofsky 40–50. The patient was wearing incontinence pads. She ate only mixed, homogenized foods five times a day and her fluid intake was estimated to be approximately 1 L a day.

Her abdominal pain, nausea and vomiting were initially treated with tramadol 20 mg and hyoscine buthylbromide 8 mg SC every 4 hr with 8-hr intervals during the night. Other drugs comprised dexamethasone, initially 4 mg increased to 8 mg SC OD in the morning; Madopar 62.5 mg BD for her Parkinson's disease; Clomipramine 62.5 mg OD for her depressive mood and omeprazole 20 mg OD. After three months of treatment, the dexamethasone dose was reduced to 4 mg OD. The dose of tramadol was increased to 50 mg per single dose due to pain exacerbation. Due to limited fluid intake for a few days, she received 500 ml of normal saline or 500 ml multi-electrolyte fluid OD. Her bowel function was maintained with glycerine suppositories PRN. In the case of nausea or vomiting, she was prescribed promethazine 12.5 mg SC. She received hydrochlorothiazide 25 mg with amiloride 5 mg for leg oedema with good effect. Her treatment was continued; however, all drugs were administered via plastic SC needles, as formerly inserted "butterfly" metallic needles caused several inflammatory local reactions. She performed some light exercises once a week with a physiotherapist: increasing efficiency, active exercises, breathing exercises, massage of lower extremities, walking with assistance and isometric exercises. She was visited by a nurse three times a week and a physician every two weeks from the home palliative care team. She received good support from her husband and from the three adult daughters.

In spite of acceptable symptom control, she drank 0.5 L of fluids per day and her anorexia was exacerbated. Her husband was exhausted from caring for the patient. She was considered for parenteral nutrition due to low food intake and at the beginning of December 2008 she was admitted to the palliative care inpatient unit. Laboratory results showed dehydration, hypoproteinaemia, hy-

poalbuminaemia and electrolyte imbalance: hypokalaemia 2.7 mmol/L (3.7–5.2) and hypomagnesaemia 1.5 mg/dl (1.95–2.95). Her CRP was 131 mg/L (0.1–5). She continued the home drug regimen with added intravenous fluids (1.5 L/day with potassium and magnesium) with dexamethasone 4 mg IV once daily. The water and electrolyte imbalance was corrected and a central venous access created. However, after a five-day stay in the palliative care unit, she died suddenly before starting parenteral nutrition. The cause of death was attributed to severe cachexia.

Discussion

This case report is an illustration of problems encountered during the care of a patient with advanced gastric cancer and CACS. The patient complained of several symptoms associated with gastric cancer (nausea, epigastric pain with belching and lack of appetite) but also of the delayed diagnosis and associated spiritual pain. The latter problem was associated with the fact that the investigations performed during a year before diagnosis establishment did not show cancer presence. In addition, the progressive CACS resulted in intense psychological distress. Despite support from the home palliative care team, the family nurse and all family members, it was necessary to admit the patient to the inpatient palliative care unit for respite care, as her husband was exhausted from taking care of the patient. Although the patient did not agree to a gastrostomy and/or stent insertion [7], several oesophagus and cardia endoscopic dilatations allowed the maintenance of feeding orally. These interventions can improve patient QOL [8].

The management of patients with advanced GI tumours is a challenge for clinicians as, apart from primary cachexia, the secondary malnutrition associated with cancer progression and symptoms of GI obstruction contribute to the CACS development; this seems to have been the case in our patient [9]. The patient was treated with corticosteroids and did not receive progestagens because of the secondary cachexia, dysphagia and nausea. The psychological and spiritual distress added to this and, apart from comprehensive medical management, psychosocial and spiritual support is needed for such patients and their families [10]. Apart from the support of the nurses, physicians and a psychologist, the patient performed light exercises intended for the decrease of fatigue intensity and the improvement in functioning and mood, with some benefit achieved as reported in the literature [11]. As mentioned, the patient was admitted to the palliative care unit for respite care for her husband and considered for a parenteral nutrition programme due to significant exacerbation of her anorexia. However, due to sudden death, this approach was not introduced and she only received intravenous fluids. The cause of this unexpected patient death was attributed to severe cachexia. However, as the patient died suddenly, other potential pathologies, such as myocardial infarction, heart failure exacerbated by fluid administration, pulmonary embolism, reflex bradycardia secondary to oesophagus distension, and infection from the central catheter, should be considered. Unfortunately, this can only be speculated upon, as an autopsy was not conducted.

Cachexia often accompanies loss of appetite (anorexia) and weakness (asthenia) and is called cachexia-anorexia-asthenia syndrome by some [12]. The main symptoms of CACS are loss of appetite, loss of weight, early satiety, general weakness, frequent fatigue, decrease in immunology system function and metabolic disorders [13, 14]. Cachexia management comprises pharmacotherapy and nutritional support, anticancer treatment (if possible), the management of numerous symptoms that may contribute to cachexia development, as well as psychosocial and spiritual support for the patient and family [15]. The aim of the treatment is to inhibit anorexia and weight loss as quickly as possible, to sustain a good sensation of well-being and general condition, and to inhibit or delay disturbances in the immunology system. The application of light exercises may decrease fatigue intensity and improve functioning and patient mood [11]. The treatment should start with information on CACS and its management possibilities being provided to the patient and family. Another aim is appetite improvement through the treatment of the reversible causes of appetite loss. Several factors may cause lack of appetite, such as dry and sore mouth, the adverse effects of drugs (opioids, antycholinergics, SSRIs, antibiotics), the adverse effects of chemotherapy and radiotherapy, especially for the head and neck regions, inadequate pain relief, and other symptoms, such as dyspnoea, nausea and vomiting [5]. In the case of mechanical obstruction of the upper GI tract, a gastrostomy or jejunostomy may be considered, provided the patient has a relatively good general condition [16]. A stent [7] or nasogastric tube may be inserted, although the latter should be limited to a short period of time (4–6 weeks) [17].

The drugs that show efficacy in the pharmacotherapy of CACS are progestagens (megestrol acetate, medroxyprogesterone acetate) [18]. However, these

agents increase body weight, improve well-being, appetite and quality of life, whilst failing to increase lean body mass, an important target of CACS management [19]. Other commonly-used drugs are corticosteroids (dexamethasone, prednisolone, methylprednisolone) and prokinetics (metoclopramide, domperidone). However, similarly to cannabinoids, their role is still not clearly established [20] and the latter are unavailable in Poland. Other drugs are being assessed in clinical trials. Preliminary results have demonstrated that a combination of megestrol acetate and olanzapine may be much more effective than progestagens administered alone [21]. The administration of selective COX-2 inhibitors (e.g. celecoxib), oxandrolone, thalidomide, EPA (eicosapantaenoic acid), ghrelin mimetics, insulin, and ostarine (the first-class selective androgen receptor modulator SARM) are newer and promising therapies. An experimental approach to CACS management in mice comprises myostatin antagonism, antagonists of the melanocortin MC4 receptors that can be administered orally, CD+ T cells and branched-chained amino acids [22]. A combination of different approaches is more effective than a single method of treatment. A combination of megestrol acetate with ibuprofen improved quality of life and was more effective than megestrol with placebo in patients with weight loss in the course of gastrointestinal cancer [23]. Preliminary results achieved in 125 patients in a phase III study indicate that combining progestagens with EPA, L-carnitine and thalidomide was more effective than using any of these agents alone [24].

The nutritional support is also an important part of CACS management, especially for patients with GI tract tumours and secondary cachexia. For those who can use the oral route, the addition of high energy supplements may improve the calorie intake. In the case of dysphagia, enteral feeding with oesophagus or cardia tumour stents should be considered [25]. In patients with GI obstruction, parenteral nutrition may be considered but it is associated with numerous possible complications and high financial costs [26, 27]. In a recent study parenteral nutrition in patients with incurable GI cancer prolonged survival but with frequent infectious complications; there is no tool to predict which patients may receive benefits which outweigh the complications [28].

Future studies may address the cytokine genetic polymorphisms associated with CACS. In 203 patients with gastro-oesophageal cancer, single nucleotide polymorphism was performed. Compared with other genotypes, the IL-10 GG genotype retained an independent association in determining the extent of weight loss upon multivariate analysis (95% CI: 0.52, 3.43; $p = 0.008$). Possession of the GG allele was associated with a 2.3 times increased risk of developing cachexia (95% CI: 1.2, 4.3; $p = 0.014$). It was suggested that the IL-10 genotype of a patient can influence the development of cachexia among patients with gastroesophageal malignancy [29]. In a preliminary study, 471 patients with non-small cell lung cancer were explored as to whether any of the 22 single nucleotide polymorphisms of inflammatory cytokines (IL-1 beta, IL-1RN, IL-6 and tumour necrosis factor alpha) is associated with anorexia and weight loss. Only tumour necrosis factor alpha rs800629 was associated with anorexia ($p < 0.001$). Cancer stage and the patient's age were the only predictors of survival [30].

The management of CACS remains a challenge for palliative care teams. New, more efficient therapies are eagerly awaited, as current available measures are often ineffective. A holistic approach with medical, nutritional, psychosocial and spiritual support for patients suffering from CACS is currently recommended.

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