J Cancer Res Clin Oncol (1986) 111: 82–85

Journal of Cancer Research and Clinical Oncology

Short Communication

Brown Adipose Tissue in Cancer Patients: Possible Cause of Cancer-Induced Cachexia

Frank G. Shellock, Mary S. Riedinger, Michael C. Fishbein

Cedars-Sinai Medical Center and UCLA School of Medicine, Division of Cardiology, Department of Medicine, 8700 Beverly Boulevard, Los Angeles, California 90048, USA

Summary. Cachexia is a common manifestation of advanced cancer and frequently contributes to physical disability and mortality. An increased metabolic rate has been suggested to be one of the causes of cancer-induced cachexia, although the mechanisms producing this hypermetabolism remain unclear. The presence and activation of brown adipose tissue, a highly thermogenic tissue, may result in a hypermetabolic state and be partially responsible for weight loss in cancer patients. To investigate this hypothesis, we examined necropsy samples of peri-adrenal tissues using light microscopy to identify the prevalence of brown adipose tissue in 25 cachectic patients who died from cancer and 15 age-matched subjects who died from other illnesses. Brown adipose tissue was observed in 20 of the cancer patients (80%) compared to 2 of the age-matched subjects (13%). Therefore, our preliminary results indicate that a high prevalence of brown adipose tissue is associated with cancer-induced cachexia and may reflect an abnormal mechanism responsible for profound energy expenditure and weight loss.

Key words: Brown adipose tissue – Cachexia – Cancer

Introduction

Cachexia is a common manifestation of advanced cancer and contributes substantially to physical disability and mortality (Theoglides 1979). Despite the site or type of tumor, cachexia is a frequent cause of death (Strain 1979; Theoglides 1979; Warren 1932). There are several factors which are thought to be responsible for cancer-associated cachexia. Some of these factors include nutritional disturbances such as anorexia and malabsorption due to chemotherapeutic agents, radiation therapy, and neoplasms themselves (Theoglides 1979). Ectopic hormone production by tumors has also been shown to interfere with normal metabolism (Strain 1979; Theoglides 1979). Increased metabolic rate and an elevated energy expenditure are commonly observed in cancer patients (Strain 1979; Theoglides 1979; Warnold et al. 1978). Mechanisms responsible for this accelerated metabolism remain unclear.

The metabolic activity of brown adipose tissue is substantially higher than that of white adipose tissue (Rothwell and Stock 1984). Brown adipose tissue has been implicated as an important effector of both body temperature and energy balance in many mammals as well as man (Rothwell and Stock 1984). Rothwell and Stock (1984) have suggested that there may be a causal relationship between the elevated metabolic rates that are typically observed in human cancer patients and the presence and activation of this highly thermogenic tissue. In an animal model of cancer-induced cachexia, Brooks et al. (1981) observed that there was a profound weight loss in tumor-bearing rats due to a high metabolic rate produced by the activity of brown adipose tissue. Therefore, this investigation was designed to identify the prevalence of brown adipose tissue in patients with cancer-induced cachexia.

Methods and Materials

Consecutive autopsy reports and hospital records were reviewed to identify two group of subjects: Group-I, adults who died of cancer and who were cachectic at the time of their death; Group-II, age-matched individuals who died from other illness without any prior history of neoplastic disease or the presence of cachexia. Subjects with pheochromocytoma, history of hypothermia, or previous prolonged cold-exposure were excluded from this study since brown adipose tissue is typically associated with these conditions (Hassi 1977; Tanuma et al. 1975, 1976). The presence of cancer was determined from the pathological findings at autopsy. Cachexia was

Offprint requests to: Frank G. Shellock

* Supported in part by NIH-NHLBI, NRSA, PHS-2271 & HL07338-05

Table 1. Descriptive data for group-I study subjects

	Age (yrs)	Sex	Ht (cm)	Wt (kg)	Diagnosis	BAT
1.	87	F	170	45	Hepatocellular carcinoma	Yes
2.	70	F	160	50	Undifferentiated malignant neoplasm, thyroid	No
3.	72	F	173	50	Adenocarcinoma, endometrium	Yes
4.	54	F	166	48	Adenoepidermoid carcinoma, uterine	Yes
5.	82	F	155	50	Adenocarcinoma, endometrium	Yes
6.	84	F	165	68	Adenocarcinoma, endometrium	Yes
7.	87	M	188	78	Adenocarcinoma, pancreas	Yes
8.	69	M	175	55	Adenocarcinoma, lung	No
9.	70	M	175	53	Adenocarcinoma, pancreas	No
10.	82	F	152	35	Anaplastic carcinoma, lung	Yes
11.	62	F	155	43	Hemangiopericytoma, thigh	Yes
12.	65	F	160	38	Sarcoma, intra-aortic	Yes
13.	86	M	175	59	Adenocarcinoma, recto-sigmoid	No
14.	74	F	163	44	Adenocarcinoma, lung	Yes
15.	80	F	155	46	Adenocarcinoma, ovary	Yes
16.	67	F	165	57	Adenocarcinoma, stomach	Yes
17.	75	M	165	64	Adenocarcinoma, colon	No
18.	55	F	152	29	Squamous cell carcinoma, cervix	Yes
19.	71	M	170	49	Stage C transitional cell carcinoma, bladder	Yes
20.	65	F	168	47	Adenocarcinoma, kidney	Yes
21.	46	F	160	51	Adenocarcinoma, lung	Yes
22.	53	F	145	41	Adenocarcinoma, ovary	Yes
23.	77	F	165	45	Adenocarcinoma, pancreas	Yes
24.	76	F	152	54	Lymphoma	Yes
25.	80	F	157	45	Adenocarcinoma, pancreas	Yes
$n=25$	72 ± 11	M:F 6:19	163 ± 10	50 ± 10		Y:N 20:5

(Values = mean ± SD, Ht = height, Wt = weight, BAT = brown adipose tissue)

Table 2. Descriptive data for group-II study subjects

	Age (yrs)	Sex	Ht (cm)	Wt (kg)	Diagnosis	BAT
1.	74	M	180	89	Sepsis	Yes
2.	45	M	183	99	Multiple trauma	No
3.	78	F	155	60	Ruptured aneurysm	No
4.	49	M	163	78	Acute MI	No
5.	74	F	160	70	Acute MI	No
6.	65	F	160	70	Acute MI	No
7.	73	M	163	66	Cerebral infarct	No
8.	63	F	160	52	Pneumonia	No
9.	61	M	175	66	Ruptured aneurysm	No
10.	62	F	152	81	Acute MI	No
11.	68	M	168	94	Pulmonary emboli	No
12.	64	M	168	77	Pulmonary emboli	No
13.	50	M	191	83	Ruptured aneurysm	Yes
14.	87	M	172	77	Sepsis	No
15.	74	M	160	68	Acute MI	No
$n=15$	66 ±12	M:F 10:5	168 ±10	75 ±13		Y:N 2:13

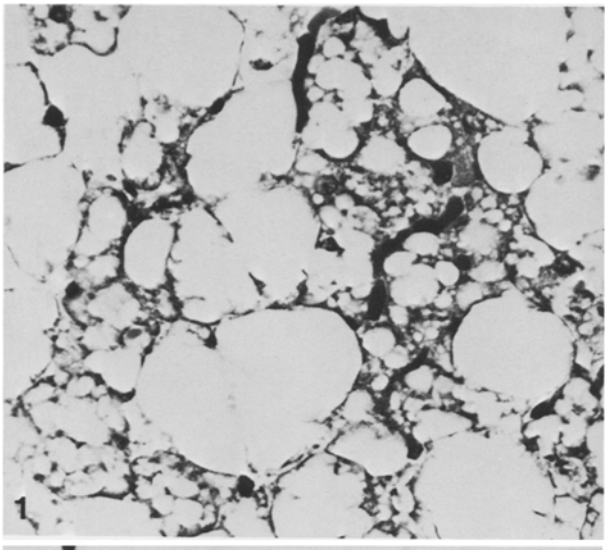
(Values = mean ± SD, Ht = height, Wt = weight, BAT = brown adipose tissue, MI = myocardial infarction)

determined from the physical description of the patient (i.e., height and weight) as well as based on the opinion of the examining pathologist.

Necropsy sections of fat were selected for retrospective evaluation from the peri-adrenal area because it has been demonstrated that brown adipose tissue may persist in this anatomical site until the latest decades of life (Hassi 1977; Heaton 1972; Tanuma et al. 1975, 1976). The histological sections were prepared by fixation of tissues in 10% formalin, processing in graded alcohols, embedding in paraffin, sectioning at 5 μm, and staining with hematoxylin and eosin. The slides of necropsy tissue were "blinded" as to patient identity and diagnosis and were examined under conventional light microscopy by two observers. The identification of brown adipose tissue was based on the following established histological criteria (Lindberg, 1970): multilocular cells, eosinophilic granular cytoplasm, centrally located oval nuclei, and distinct cell borders with numerous lipid vacuoles.

Results and Discussion

Tables 1 and 2 display descriptive data and other pertinent information on the subjects in this investigation. Although our study population represented a variety of neoplasms it should be noted that, in humans, weight loss does not correlate with the type of



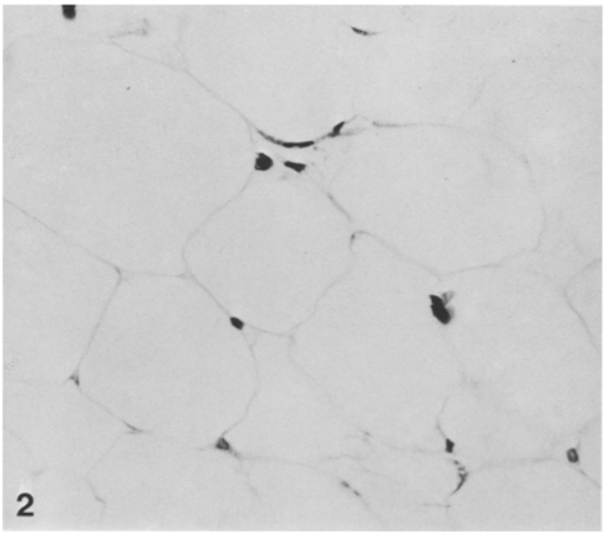


Fig. 1. Photomicrograph of brown adipose tissue obtained from the peri-adrenal area of a 75-year-old male subject who died from adenocarcinoma of the colon. Note the cytoplasmic-rich multiocular brown adipocytes interspersed with monocular white adipocytes. Hematoxylin and eosin stain, original magnification × 100

Fig. 2. Photomicrograph of white adipose tissue obtained from the peri-adrenal area of a 62-year-old subject who died from an acute myocardial infarction. Note the monocular appearance of the white adipocytes. Hematoxylin and eosin stain, original magnification × 100

cancer, duration of disease, or with the site and number of metastases (Cohen et al. 1978). In Group-I, of the 25 patients who died from cancer and who were cachectic at the time of their death, 20 (80%) exhibited multilocular eosinophilic adipocytes with granular cytoplasm indicative of brown adipose tissue in their peri-adrenal necropsy samples. In addition, all samples of brown adipose tissue from these patients displayed a heterogenous histological appearance (i.e., mixture of unilocular and monolocular cells) which suggests that this tissue had the potential of being thermogenically active (Tanuma et al. 1975, 1976). An example of brown adipose tissue found in one of these subjects is displayed in Fig. 1. In comparison, only 2 of the 15 age-matched subjects who died from illnesses without prior history of cancer or cachexia had brown adipose tissue (Table 2), 1 patient died from sepsis and the other from a ruptured aneurysm. Only white adipose tissue (Fig. 2) was observed in the histological sections from the remaining 13 patients.

Brown adipose tissue is typically located in definite anatomical sites in humans primarily during the early stages of life and gradually diminishes with age. It is interesting to note that we identified a high incidence of brown adipose tissue in a relatively old population (i.e., 72 ± 11 years) of patients with cancer and cachexia compared to the low incidence of this tissue we found in the age-matched subjects who died from other illnesses. Other reports of the prevalence of brown adipose tissue in an adult population of a comparable age range who died with a variety of diagnoses (including cancer) have demonstrated as high as a 40% occurrence (Tanuma et al. 1975, 1976). A possible limitation of this study is that we did not determine the incidence of brown adipose tissue in a control group of cancer patients who died without cachexia. We were unable to acquire this information because of the relatively few age-matched subjects we could categorize in this patient group.

We made no attempt to quantify the amount of brown adipose tissue in the subjects of this study. However, because of the highly metabolic nature of this tissue (i.e., in vivo aerobic capacity estimated of heat produced at a rate of 500 W/kg, Foster and Frydman 1978), even a small amount could account for a substantial increase in overall metabolism. Therefore, the finding of a high prevalence of brown adipose tissue in patients dying with cancer-induced cachexia suggests that this tissue may be partially responsible for an accelerated rate of energy expenditure and resultant weight loss. Although profound weight loss in cancer patients may be due to a variety of etiologies, we feel that further studies are warranted to define the role of brown adipose tissue in this patient population.

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Received July 29, 1985/Accepted October 21, 1985