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Sudden Tumour Regression With Enhanced Natural Killer Cell Accumulation in a Patient With Stage IV Breast Cancer

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Spontaneous regression of advanced breast cancer is a rare phenomenon. Efforts have been made in order to explain it by means of immunological mechanisms. Corticosteroids have demonstrated important efficacy in the treatment of breast cancer. We present a patient with stage IV breast cancer in whom large tumour masses dramatically regressed during treatment with dexamethasone alone. In this patient, histological and hormonal findings, with results of analyses on surface and intracellular blood cells markers demonstrated significant redistribution of lymphocytes and accumulation of natural killer cells in tumour masses. It seems that dexamethasone has acted through the hypophyse against cancer.

Key words: spontaneous regression, breast cancer, dexamethasone, surface and intracellular markers, natural killer cells

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INTRODUCTION

SPONTANEOUS REGRESSION in metastatic cancer is a very rare event reported in the literature as case reports. Its occurrence has been estimated to be less than 1 in 100 000 cases [1]. Although this phenomenon has remained an enigma, efforts to explain its mechanism and characteristic features have focused on non-specific stimulation of the immune system [2].

Endocrine therapy has been found to be an important therapeutic option in the treatment of breast cancer. It has, for instance, been observed that after removal of the ovaries in premenopausal women the disease has regressed [3]. Also, similar responses following adrenalectomy or hypophysectomy in postmenopausal women have been observed [4]. Furthermore, other hormones such as progestins, androgens and corticosteroids have also demonstrated antitumour effect [5–8].

Corticosteroids have been used either as primary treatment or in combination with other therapies in the treatment of breast cancer. When prednisolone alone has been given, an objective response rate of no more than 14% has been achieved [5]. When corticosteroids were combined with other endocrine treatments after mastectomy and radiotherapy in early breast cancer, significant reductions in local recurrence rates and prolonged survival rates were achieved [9].

In advanced cases, dexamethasone has been found to be useful in relieving acute symptoms caused by brain metastases or by tumours compressing the spinal cord. Dexamethasone successfully prevents adverse effects such as tissue oedema caused by radiotherapy.

The disadvantages of dexamethasone and other corticosteroids are their various side-effects, such as hypertension, peptic

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ulceration, mental hyperexcitability and metabolic disturbances. It has also been demonstrated that hydrocortisone can lead to lymphocytopenia, which reaches its maximal effect 6 h after administration [10]. It is known that lymphocytes can redistribute from the peripheral blood to other tissues [11]. Therefore, it is conceivable to assume that corticosteroids could cause redistribution of lymphocytes to lymph nodes and tumour tissues.

Physicians have very rarely the opportunity to meet a patient with advanced breast cancer whose tumours start to regress rapidly with such a treatment as dexamethasone. We are presenting such a case in this paper. The unusual amount and methods of examination with the close follow-up of this patient were dictated by the rarity of the case.

CASE REPORT

During the spring of 1992, a 46-year old woman noticed a mass in her right breast, but she did not seek any medical examination. One year later, at the beginning of May 1993 she was admitted to hospital in acute psychosis which was rapidly followed by unconsciousness. A T4 partly necrotic breast tumour was found on the right side of the chest wall comprising the whole right breast and surrounding tissues. Enlarged lymph nodes were palpable in the right axilla. The primary tumour also invaded the sternum, growing through the chest wall. Another metastatic tumour was found in the clavicular region (Figures 1, 2 and 3). The psychosis was probably caused by multiple brain metastases demonstrated by computer tomography (CT) scans. Additionally, CT examination demonstrated hydrothorax on both sides.

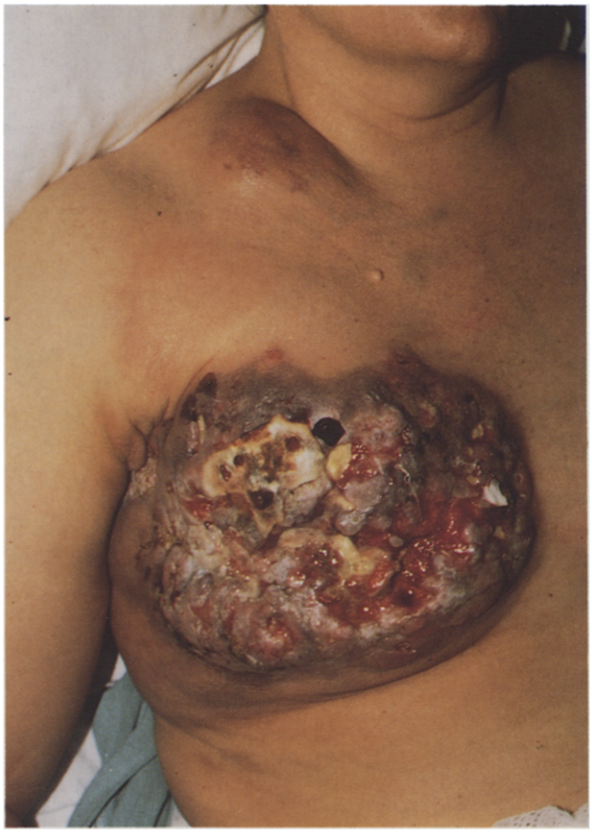

Figure 1. A T4 tumour comprising the whole right breast and another tumour in the clavicular region are seen.

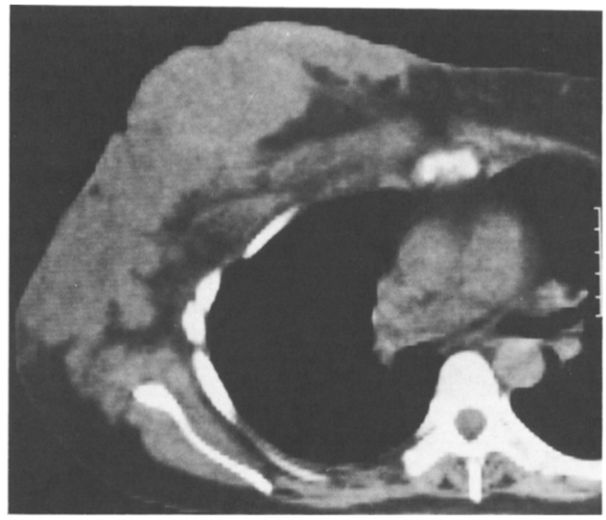

Figure 2. Unenhanced CT scan obtained at the same time shows the massive breast tumour with infiltrative growth into the right axilla.

On 7 May, when the patient was still unconscious, dexamethasone 5 mg three times a day was started, administered as intramuscular injections, and later on, when the patient became able to take oral nutrition, dexamethasone was administered orally. The indication for dexamethasone was the increased intracranial pressure caused by multiple brain metastases. Radiotherapy for brain metastases was started on 12 May and given 3 Gy daily, five fractions per week with a total of 30 Gy for over a period of 2 weeks. Histological biopsies from the primary tumour, from the axillary nodes and from the metastasis in the clavicular region demonstrated advanced adenocarcinoma of the breast. A bone isotope scan and X-rays demonstrated several bone metastases.

During radiotherapy, the patient's general condition

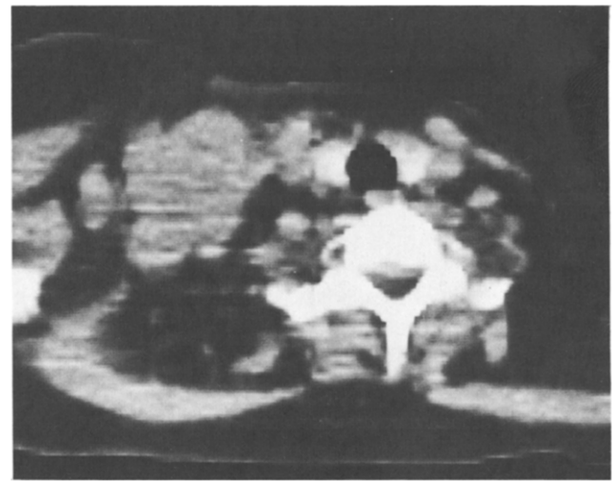

Figure 3. Unenhanced CT scan showing the large metastatic tumour in the clavicular region.

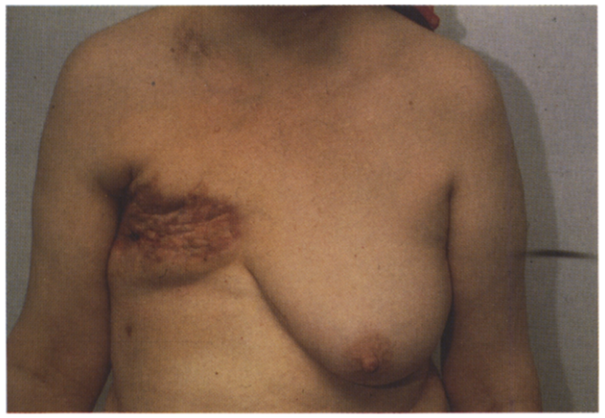

Figure 4. After 5 months of treatment with dexamethasone alone, both the primary tumour and metastasis in the clavicular region have dramatically regressed.

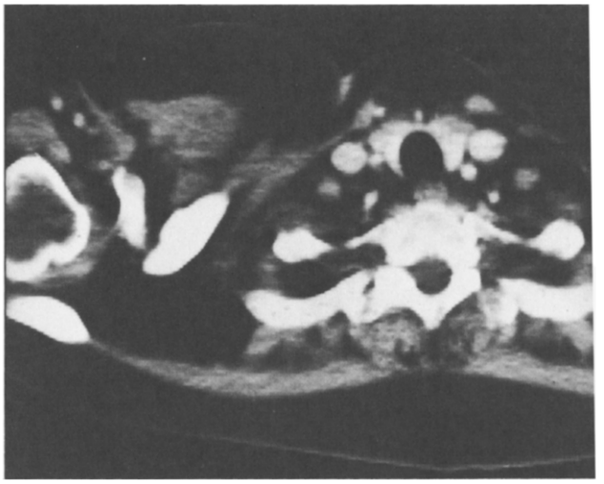

Figure 6. Contrast-enhanced CT image at the same section level as in Figure 3 demonstrates the regression of the tumour in the clavicular region.

improved dramatically and within 2 weeks after conclusion of radiotherapy the patient became rational. The size and shape of both the primary tumour and the palpable metastases decreased continuously and rapidly. This advantageous phenomenon was explained to the patient who accepted that in these conditions, dexamethasone doses of 3 mg three times a day should be continued with no further treatment. She was informed about the usual treatment of advanced breast cancer. The patient's general condition and tumour response were followed daily and later, weekly. CT scans and photographs of the chest wall and laboratory examinations were performed regularly. The regression was seen both in the primary tumour and metastases (Figures 4 and 5).

On 2 July, the patient's general condition improved considerably and she became able to manage alone at home. As the pain caused by bone metastases disappeared, no pain-relieving medication was needed. Repeated isotope bone scans revealed a slight unusual regression in bone metastases. She was closely followed as an outpatient.

Response to treatment with dexamethasone continued until the end of September 1993, when the disease remained stable. Daily doses of dexamethasone were then reduced in order to avoid possible adverse effects. Treatment with tamoxifen (40 mg/day) was started. In November 1993, the disease still remained stable.

In order to establish the possible causes of such dramatic regression, the following routine and special laboratory investigations were performed.

Tumour markers

At the time of diagnosis, plasma carcinoembryonic antigen 15-3 (CA 15-3), carcinoembryonal antigen (CEA) and tumour-associated trypsin inhibitor (TATI) were increased, at levels of 147 kU/l, 12.5 μg/l, and 25.1 μg/l, respectively. Five months later, in September 1993, CA 15-3 was normal while CEA and TATI values remained unchanged, ranging between 8.4–15.9 μg/l and 19.2–25.1 μg/l, respectively. Other tumour markers such as neuron-specific enolase (NSE), CA19-9 antigen, CA-50 antigen and CA-125 antigen were and remained normal.

Hormonal findings

At the time of diagnosis, the patient has amenorrhea. Plasma adenocorticotropin (ACTH) value, 5 ng/l, was lower than normal at the time of diagnosis and remained unchanged as controlled in September 1993. Testosterone, oestradiol and oestrogen were and remained normal. Plasma luteinising hormone (LH) and progestin were and remained also normal. Plasma cortisol was lower than normal, 29 nmol/l. Both oestrogen and progestin receptors were mostly negative.

Histological findings

Adenocarcinoma tissue with strong pleomorphy and enhanced lymphocyte reaction was seen both in primary tumour and metastases. In deeper tissue, less lymphocytes and more fibroblasts were seen. Immunohistochemical examination demonstrated that only 20% of tumour cells were oestrogen receptor-positive whereas only few cells were progestin receptor-positive. In August 1993, biopsy from the primary tumoural region showed no malignant cells but a great number of fibroblasts and inflammatory cells. However, some atypical cells were seen, but

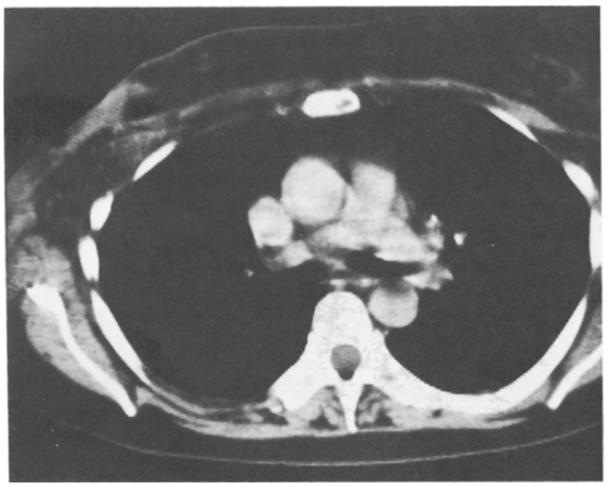

Figure 5. Contrast-enhanced CT image at the same section level as in Figure 3 demonstrate the regression of both tumours seen in Figures 1, 2 and 3.

Table 1. The immunophenotype of tumour-infiltrating lymphocytes and antigens of stroma in skin biopsy

Antigen	Lymphocytes	Carcinoma cells	Blood vessels endothelium	Stroma
CD2	++	–	–	–
CD3	+	–	–	–
CD4	+	–	–	–
CD8	+++	–	–	–
CD11b	++++	–	–	++++
CD16	++++	+/–	–	++++
CD19	+/–	–	–	–
CD20	–	–	–	–
CD25	+	–	–	–
CD49d	+	–	–	++
ICAM-1	+++	–	++++	+++
Class II	+	–	–	+

it was difficult to establish whether they were malignant or inflammatory.

Flow cytometry

Flow cytometry performed with fresh samples demonstrated a small sub-population of aneuploid cells with a DNA index of 0.83, indicating hypoploidy, although almost all cells were diploid.

Surface and intracellular markers

The subclasses of peripheral blood lymphocytes were clearly abnormal (Table 1). The relative amount of B cells was remarkably increased up to nearly 40%, whereas about 60% of lymphocytes were CD2+/CD3+ T cells. The amount of CD4+ T helper cells, 49%, was normal, but CD8+ T cells were diminished to 19%. The CD4/CD8 ratio was 2.6. The leukocyte surface antigens associated with the natural killer (NK) subclass, such as CD16, CD56 and also CD11b were expressed in low amounts in peripheral blood lymphocytes, indicating that NK cells were not in peripheral blood circulation. The expression of CD25 (interleukin-2 receptor) and ICAM-1 (CD54) was low in peripheral lymphocytes, whereas the expression of MHC class II DR was increased due to a higher amount of B cells.

The biopsy was taken from subcutaneous metastasis in the supraclavicular area. It was histologically characterised by tissue containing clustered neoplastic tumour cells and lymphocyte infiltrations. The endothelium in blood vessels expressed ICAM-1 in great amounts. The analysis of tumour-infiltrating lymphocytes showed an opposite pattern of antigen expression than in peripheral blood (Table 2). There were few CD19+ or CD20+ B cells and CD4 T cells, whereas the number of CD8+ T cells, CD16+ and CD11+ lymphocytes was increased. CD25 (IL-2 receptor) and MHC class IIDR were expressed in low amounts in lymphocytes, whereas ICAM-1 expression was rather high. In addition, the non-cellular stroma showed intensive expression of CD11b and CD16. In June 1993, the relative amount of B

Table 2. Peripheral blood lymphocyte subpopulations of the patient at the time of skin biopsy in May 1993 and 1 month later in June 1993

Subpopulation	CD antigen	Antibody	% in May 1993	% in June 1993
Control		NIL	0.6	0.3
Control	2	MSIGGFITC	2.4	2.7
T cells	3	OKT-11	59	65
T cells	4	OKT-3	59	64
T helper cells	8	OKT-4	49	53
T supressor cells	20	OKT-8	19	13
B lymphocytes	19	B-1	36	23
B lymphocytes	16	B-4	38	n.d.
Other	56	CD-16	3	9
LGL (NK) cells	54	CD-56	1	4
Other	25	ICAM-1	9	12
AKT-T cells		IL-2res	0.2	5
Other		ClassIIDr	31	n.d.
Other	11b	CD-49d	60	n.d.
Other	30	CD-11b	15	n.d.
Other		BERH2	0.3	n.d.

n.d., not defined.

cells was diminished, and the number of NK-associated antigens was increased from a very low level up to 9%.

DISCUSSION

Our case does not meet with the criteria of spontaneous regression, as the patient received a therapy that has established cytotoxic effect on tumours. On the other hand, it is difficult to estimate what would have been the outcome without dexamethasone treatment. Before the treatment, the cancer progressed into a very advanced stage both locally and by developing large metastases in several sites. During the treatment with dexamethasone, regression of tumours was obvious as established by photographs and CT scans. Response to dexamethasone was also shown by some tumour markers. CEA normalised completely during the treatment, while CA-15-3 and TATI remained relatively unchanged.

There are difficulties in explaining the importance of hormonal findings in the regression of the disease. Low values of ACTH and cortisol were probably caused by diminished function of the hypophyse. This could allow us to assume that, through the hypophyse, dexamethasone and perhaps other corticosteroids, could have some antitumour effect.

In breast cancer, DNA aneuploidy is a sign of poor prognosis. In this case, however, the majority of the cell population was diploid. The subpopulation of aneuploid cells with DNA index of 0.83 was an indication of hypoploidy and a criteria for better prognosis.

The loss and redundancy of NK cells and CD8+ T supressor lymphocytes in the blood and their simultaneous infiltration into the tumour tissue were noticed in the immunological specimens [12]. These observations are in accordance with the data in the literature [11] that corticosteroids can redistribute lymphocytes from the circulation to other sites. It is clear that the tumour masses diminished during the dexamethasone treatment, but it is still unclear whether dexamethasone alone was enough to introduce such a response. At the same time, NK cells accumulated around the tumour. On the other hand, similar types of high concentration could be induced by adrenalectomy or oophorectomy. Indeed, our patient perhaps experienced both.

Prolonged use of corticosteroids could induce serious side-effects. Nevertheless, a relatively long period (4 months) of continuous treatment with daily doses of 9 mg of dexamethasone was used in this patient without the emergence of side-effects.

Corticosteroids are, for instance, sequentially used in the treatment of malignant lymphomas with no remarkable adverse events reported. Protection of these patients against peptic ulcers caused by corticosteroids, cytostatics or a combination of both is actually efficacious.

The overall response rate for hormonal therapy in oestrogen receptor-negative patients varies between 6 and 10%, independently of the modality of treatment [13]. Presently, hormonal status and hormonal receptors in patients with breast cancer are routinely established allowing possibilities to determine which groups of patients could benefit from hormonal adjunct. Surface and intracellular markers could be important in the definition of such groups. Trials are needed in order to determine which patients with breast cancer could benefit from the addition of dexamethasone or other corticosteroids to the usual antineoplastic treatment. A pilot trial including adjuvant use of dexamethasone for patients with breast cancer is already planned to be conducted in the Department of Radiotherapy and Oncology of Helsinki University Central Hospital.

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