Metastatic Breast Cancer Presenting as Fever, Rash, and Arthritis

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Background. Fever can be the presenting symptom of metastatic breast carcinoma, but the combination of fever, polyarthritis, and an erythematous rash as a paraneoplastic syndrome in breast carcinoma is very rare.

Methods. The clinical course of a 49-year-old female with a history of ductal breast carcinoma who presented with fever of unknown origin, polyarthritis, and an erythematous rash is described. Moreover, cytokine measurements were performed.

Results. Initially, despite extensive evaluation, a diagnosis could not be made. Six weeks after the onset of symptoms, a right axillary lymph node became palpable and the diagnosis of relapsing breast carcinoma was made. Chemotherapy led to defervescence and disappearance of the symptoms. Elevated interleukin-6 and interleukin-1 receptor antagonist concentrations were found.

Conclusion. To the authors' knowledge, the severe paraneoplastic signs encountered in this patient have not been described in breast carcinoma. The presentation is even more remarkable in view of the relatively small visible tumor mass. Cancer 1995;75:1608-11.

Key words: fever of unknown origin, breast carcinoma, arthritis, skin lesions, cytokines.

Introduction

Fever is a well recognized presenting symptom of neoplastic disease. It has been described in Hodgkin's disease, leukemia, renal cell carcinoma, and other malignancies. The diagnosis of neoplastic fever can be notoriously difficult and in the course of the diagnostic process, many patients fulfill Peterdorf's criteria for fever of undetermined origin. Fever as an accompanying symptom in breast cancer is rare despite the high incidence of the disease. Other symptoms, such as skin lesions, disturbances of liver enzymes, and joint involvement are clinical expressions of a heterogeneous group of systemic, infectious, and rheumatic illnesses. Although this group of symptoms may be a feature of malignant disease, we have not been able to find this combination in association with breast cancer. We describe a female who presented with fever of undetermined origin, polyarthritis, and an erythematous rash that was associated with a relapse of an initially small, metastatic breast carcinoma.

Case Report

A 49-year-old postmenopausal woman was referred to our hospital in June 1992 because of intermittent fever, polyarthralgias, and urticarial rash of 3-week duration. Her medical history revealed a bulging disk in 1988 that was treated conservatively. In March 1991, she developed a ductal carcinoma of her right breast with positive axillary lymph nodes (cT2N1M0, pT2N1M0). Treatment was delivered by lumpectomy and locoregional irradiation (50 Gy). She was admitted and a 4-week thorough investigation, including computed tomography scanning of thorax and abdomen, was performed. No evidence of infectious disease, autoimmune disorder, or malignancy and especially, recurrence of breast cancer could be established. Various antibiotics were prescribed without amelioration of the clinical symptoms. Because she fulfilled the criteria of Medsger, a tentative diagnosis of adult-onset Still's disease was considered and she was given indomethacin 200 mg daily and naproxen (4 × 250–500 mg) thereafter. Despite this treatment she continued to suffer from polyarthralgias, chills, and high spiking fever. No diagnosis could be made and she was discharged without an established cause for her fever. Two weeks after discharge she was readmitted and on physical examination an ill, dyspneic female was seen with a generalized persistent pruritic rash and palpable erythematous noduli on the lower legs. A severe poly-
Arthritis was present and symmetrically affected the knee, ankle, wrist, elbow, and shoulder joints. Careful examination further revealed a discrete left supraclavicular (0.5 cm) and a right axillary lymph node (1 cm) not present on earlier occasions. There was no palpable mass in either breast. She lost 6 kilos of weight from the time of the onset of her symptoms.

**Materials and Methods**

Sampling of plasma was performed using special endotoxin free tubes (Vacutainer Systems, Becton and Dickinson, Rutherford, NJ). The plasma was immediately processed to avoid ex vivo cytokine excretion. Tumor necrosis factor-α was determined by radioimmuno assay as described by Van der Meer et al. IL-1β (IL-1β) was measured by radioimmuno assay (without chloroform extraction) according to Lisi et al. Interleukin-1 receptor antagonist was determined by radioimmuno assay according Poutsiaka et al. Interleukin-6 (IL-6) was measured by an enzyme-linked immunosorbent assay as described earlier.

**Laboratory Results**

Laboratory data were as follows: erythrocyte sedimentation rate 135 mm/h, hemoglobin 4.2 mmol/l, hematocrit 0.22 1/1, white blood cell count 14.9 × 10⁹/l, platelets 732 × 10⁹/l, serum creatinine 57 μmol/l, serum albumin 22 g/l, aspartate aminotransferase 71 IU/l, alanine aminotransferase 29 IU/l, γ-glutamyl transpeptidase 69 IU/l, alkaline phosphatase 474 IU/l. Tumor necrosis factor-α was 85 pg/ml (normal, 106 ± 25 pg/ml), IL-1β was 75 pg/ml (normal, 134 ± 22 pg/ml), IL-6 was 161 pg/ml (normal, <14 pg/ml) and interleukin-1 receptor antagonist was 1300 pg/ml (normal not detectable). Rheumatoid factors were negative. A skin biopsy from the left leg showed minor perivascular lymphocyte infiltration with C3, fibrin, IgM, IgA, and IgG vessel deposits. There was no tumor invasion visible. An indium-111-IgG scintigraphy showed symmetric uptake in the affected joints suggestive of inflammation. A 99-Technetium bone scan was negative. A computed tomography scan of the thorax now revealed a pleural effusion and multiple small intrapulmonary densities suggestive of metastasis.

**Discussion**

Signs and/or symptoms that are produced at a distance from the tumor and/or metastases are referred to as paraneoplastic syndrome. These symptoms occur only in a minority (7–15%) of cancer patients and respond to treatment of the underlying malignancy. Our patient with severe paraneoplastic signs is presented for three reasons: (1) to our knowledge, the impressive paraneoplastic symptoms never have been described in metastasized breast carcinoma; (2) the extent of the paraneoplastic symptoms is remarkable considering the relatively small detectable tumor mass; and (3) in cases of fever of undetermined origin, breast carcinoma as a cause should be considered. The paraneoplastic symptoms in our patient included fever, polyarthritis, an erythematous rash, liver function disturbances, and weight loss. A computer-aided search (Medline, National Library of Medicine, Bethesda, MD) using the

Chemotherapeutic treatment was initiated with oral cyclophosphamide (100 mg/m² days 1–14), 5-fluorouracil (600 mg/m² days 1 and 8), methotrexate (40 mg/m² days 1 and 8), and prednisone (30 mg/d). Treatment was complicated by a pulmonary embolus of the apical part of the left lung. The paraneoplastic signs completely disappeared in the course of 3 months. She received 9 chemotherapeutic courses in 10 months (3 cycles) and remission was achieved.

**Subsequent Course**

Twenty-four months later, in September 1994, the patient presented with a palpable mass of her right breast measuring 3.0 by 3.0 cm. A biopsy specimen was consistent with a (second) primary ductal breast carcinoma. Radiodiagnostic imaging revealed now diffuse sclerotic metastasis of the spine, pelvis, humerus, and femur, which matched with hot spots on the 99-Technetium bone scan. There were no symptoms related to the tumor and the patient specifically denied bone pain, arthralgias, fever, and skin lesions. After treatment initiation with tamoxifen (40 mg/day), within 3 days the patient developed generalized bone pain, arthralgia and later on fever and a recurrence of anemia. In view of severity of symptoms and no alleviation during 6 weeks of treatment, medication was discontinued. Evaluation revealed no tumor progression. The symptoms diminished slightly but did not disappear. The IL-1ra concentration remained elevated, with 1050 pg/ml but the IL-6 concentration was now only 22.5 pg/ml. Concentrations of tumor necrosis factor-α (65 pg/ml) and IL-1β (85 pg/ml) were normal.
higher amounts of prostaglandin-like material in vivo compared with normal breast tissue. The second primary breast carcinoma was, at time of the diagnosis, not associated with reappearance of the paraneoplastic symptoms. However, after initiation of tamoxifen treatment, fever and arthralgia reappeared. During this period, IL-1ra concentration was elevated but IL-6 concentration was only slightly increased. Our patient exemplifies the difficulties in reaching a diagnosis in case of fever of unexplained origin, even when diagnostic clues are present.

It should be emphasized that in patients with a history of cancer presenting with fever of unknown origin the diagnostic process should be first be focused on the possible recurrence of the malignancy.

**References**


