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.1,2 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.3 Fever as an accompanying symptom in breast cancer is rare despite the high incidence of the disease.2,4,5 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.6 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.7 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 in June 1992 to our hospital 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.5-11 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.5 Two weeks after discharge she was readmitted and on physical examination an ill, dyspnoeic female was seen with a generalized persistent pruritic rash and palpable erythematous noduli on the lower legs. A severe poly-
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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. Interleukin-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 × 10^9 l, platelets 732 × 10^9 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.

Treatment and Response

The right axillary lymph node was excised and the histopathologic examination was compatible with ductal breast carcinoma. Disseminated breast cancer was diagnosed and the symptoms were accounted as of neoplastic origin.

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.

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
Keywords "fever," "breast carcinoma," and "(poly)arthritis" for 1966–1993 did not yield any particular reports, emphasizing the unique presentation of our patient. Chawla et al. found only 17 patients with recurrent unexplained fever that could be interpreted as tumor-associated fever among 2400 patients with breast cancer. In only 7 patients (41%) fever was the first manifestation of recurrence of the disease, in the other 10 patients fever developed with progression of the disease. Apart from fever, there is no reference to other paraneoplastic signs in these patients with breast cancer. Whereas fever is a well recognized manifestation of occult malignancy, it is rarely accompanied by polyarthritis. The articular symptoms in our patient progressed from (poly)arthralgias to severe polyarthritis in only a few weeks. The response to the chemotherapy suggests the causal relation with breast carcinoma in our patient. Paraneoplastic acute polyarthritis is infrequent but has been recognized in squamous lung cancer and ovarian adenocarcinoma. 

In a report of 18 patients with paraneoplastic polyarthritis, only 3 were associated with breast carcinoma and other paraneoplastic symptoms were lacking. The symptoms in our patient matched the adapted criteria for adult-onset Still’s disease. It is claimed that these criteria have a sensitivity of 96.2% and a specificity of 92.1%, but the diagnosis remains to be made by exclusion as illustrated in our case. Moreover, the response to nonsteroidal antiinflammatory drugs and the evanescent maculopapular rash typical for adult onset Still’s disease were lacking in our patient. The use of naproxen in order to differentiate malignant fever from fever of other causes did not offer any clues in our patient with neoplastic fever. The usefulness of the test may be limited as it has only been studied in selected populations. The pathogenesis of paraneoplastic symptoms remains to be elucidated but in a mice model with a paraneoplastic syndrome of cachexia, hypercalcemia, and leukocytosis, tumor necrosis factor played a causal role. In our patient, we did not find an elevated tumor necrosis factor concentration in circulating plasma, but this does not exclude a role of this cytokine as a local mediator of paraneoplastic symptoms. In contrast to IL-1ß, its inhibitor (IL-1ra) was elevated and this suggest an activation of the cytokine network. In addition, IL-6 concentrations were elevated in our patient. This cytokine is a major modulator of the acute phase reaction that is characterized by fever, leukocytosis, increased vascular permeability, and elevation of acute phase proteins, all present in our patient. It remains possible that other, perhaps locally produced, inflammatory compounds are responsible for the paraneoplastic symptoms. In this respect it has been shown that breast tumors produce 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 unknown 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


