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CASE REPORT

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A case of paraneoplastic syndrome mimicking adult-onset Still's disease

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Abstract A 49-year-old woman was admitted to our hospital because of fever of unknown origin. The patient had long-lasting spiking fever, hepatosplenomegaly, pleural effusion, and skin rash. Laboratory tests showed marked leukocytosis and an extremely high serum ferritin level (240 000 ng/ml) accompanied by disseminated intravascular coagulation and hemophagocytic syndrome. Most of the patient's features were compatible with a diagnosis of adult-onset Still's disease (AOSD), the rash, however, was not a typical rheumatoid rash but multiforme erythema. Biopsy of a breast nodule revealed breast cancer, leading us to a diagnosis of paraneoplastic syndrome mimicking AOSD. Although this is a rare disorder, cases resembling the present one have been reported, indicating the importance of including paraneoplastic syndrome in the differential diagnosis of AOSD.

Key words Adult-onset Still's disease (AOSD) · Breast carcinoma · Fever of unknown origin · Hyperferritinemia · Paraneoplastic syndrome

Introduction

Neoplasms are known occasionally to cause rheumatic diseases such as dermatomyositis, polymyositis, hypertrophic osteoarthropathy, and polymyalgia rheumatica.[1,2] It is essential, therefore, to examine the presence of coexisting malignancies during the clinical evaluation of these patients. Furthermore, neoplasms may provide various manifestations whose relation with the neoplasm has not been established. Here we describe an interesting case of paraneoplastic syndrome caused by a breast carcinoma whose presentation was nearly indistinguishable from adult-onset Still's disease (AOSD). Because several similar cases have been reported in the literature,[3–8] AOSD-like paraneoplastic syndrome should be considered in the differential diagnosis.

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Case report

A 49-year-old Japanese woman with fever of unknown origin was referred to our hospital. She had a past history of fibrocystic disease in the left breast that had been resected in 1998. On May 21, 2002, she visited a local hospital because of a sore throat and slight fever. Despite treatment with antibiotics and antiinflammatory drugs, her general condition gradually deteriorated, accompanied by a high spiking fever and pleural effusion. On June 8, generalized erythema also appeared, and she was admitted to our hospital on June 11.

On admission, she was severely ill and drowsy. Physical examination showed remittent fever of up to 40.8°C, peaking in the late afternoon; cervical and inguinal swollen lymph nodes with tenderness; decreased breath sounds in the right lung; a firm, fixed 1-cm nodule with areolar retraction in the left breast, and mild hepatosplenomegaly. Erythema multiforme varying from 2 to 3 cm in diameter over the entire body, and petechiae were observed on the lower legs. Koebner's phenomenon was weakly elicited. Although arthritis was not apparent at this time, bilateral shoulder joint pain developed on the 10th hospital day.

Blood analysis showed a hemoglobin level of 8.4 g/dl, marked leukocytosis of 21 000/μl with 95% neutrophils, and a platelet count of 10.1×10^4/μl. The erythrocyte sedimentation rate was 120 mm/h, C-reactive protein 15 mg/dl, and fibrinogen 298 mg/dl. Blood chemistries were as follows: aspartate aminotransferase 208 IU/l, alanine aminotransferase 391 IU/l, lactate dehydrogenase 267 IU/l, alkaline phosphatase 265 IU/l, and creatine kinase 320 IU/l. Serological tests showed borderline antinuclear antibodies and

negative rheumatoid factor. Extremely elevated levels of serum ferritin (240000 ng/ml) and soluble interleukin-2 (IL-2) receptor (6300 U/ml) were noteworthy. Accelerated fibrinolysis was suggested by increased levels of fibrin degradation product (128 μg/ml) and D-dimer (203 μg/ml). Bone marrow aspiration revealed an M/E ratio of 20, hypoplasia of erythroid cells, slightly increased hemophagocytic macrophages, and no malignant cells. Bilateral pleural effusion was observed in the chest radiographs, analysis of which showed an exudative pattern without malignant cells. Cultures of blood, urine, and pleural fluid were negative for pathogens. Computed tomography (CT) scans of the abdomen showed mild hepatosplenomegaly, but neither lymph node swelling nor space-occupying lesions were observed.

Under the diagnosis of hemophagocytic syndrome (HPS) with disseminated intravascular coagulation (DIC), steroid pulse therapy (methylprednisolone 1000 mg/day × 3 days) followed by oral prednisolone 60 mg/day and anticoagulation were started immediately (Fig. 1). Viral infections including the Epstein-Barr virus and parvo virus B19 were excluded by serological tests.

Although the diagnosis of AOSD was indicated by these findings, the skin rash was atypical. The patient recovered from HPS and DIC over the first hospital week by responding to steroid treatment; however, her daily spiking fever remained, and severe anemia without reticulocytosis persisted, necessitating blood transfusions. The second bone marrow aspiration study conducted on the seventh hospital day showed that red blood cell aplasia and hemophagocytosis were not apparent at this time.

During the third week, results of the pathology examinations were reported. Skin biopsy showed degenerated keratinocytes with necrosis in the irregularly thickened epidermis, scattered red blood cells, and mild perivascular infiltration of lymphocytes in the dermis. In addition, biopsy of the breast nodule revealed an invasive ductal carcinoma that finally enabled us to make a diagnosis of paraneoplastic syndrome that resembled AOSD. Bone scintigraphy with ^{99m}Tc, CT scans, and brain magnetic resonance imaging (MRI) showed no evidence of metastasis except for an enlarged left axillary lymph node. Combined chemotherapy with adriamycin and cyclophosphamide followed by mastectomy left her completely asymptomatic. This normalized the acute-phase reactants, with the exception of serum ferritin, which remained at about 1000 ng/ml. She was discharged in good general condition, and took cyclophosphamide, 5-fluorouracil, and tamoxifen for 6 months. During the subsequent 1-year follow-up, there has been no recurrence of tumor or AOSD-like symptoms.

Discussion

We have described a case of paraneoplastic syndrome caused by breast cancer that closely resembled AOSD. The patient's long-lasting high spiking fever, sore throat, lymphadenopathy, splenomegaly, leukocytosis with neutrophilia, liver dysfunction, and negative rheumatoid factor were compatible with the proposed diagnostic criteria for AOSD.[9] An extremely high titer of serum ferritin was also observed, which is known to be a relatively specific finding of AOSD.[10]

The association of pleuritis, HPS, or DIC during the active phase of the disease is not unusual for AOSD.[11,12] However, the skin rash seen in this case was erythema

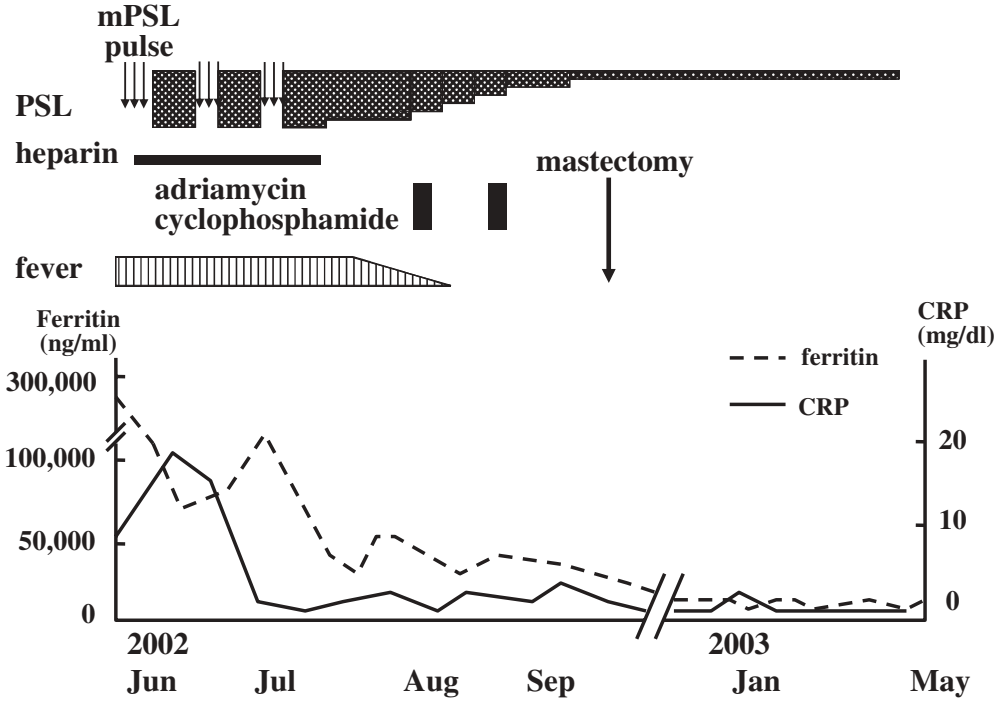

Fig. 1. Clinical course of a patient with paraneoplastic syndrome resembling adult-onset Still's disease. *PSL*, prednisolone; *mPSL*, methylprednisolone; *CRP*, C-reactive protein

Table 1. Previous reports of cases presenting AOSD-like manifestations due to paraneoplasia

Case.	Author/year	Age/sex	Causative malignancy	Described cutaneous manifestation
1	Rogues[3] 1993	52 F	Breast carcinoma	Evanescent rashes consisting of nonpruritic erythematous macules, sometimes confluent
2	Drenth[4] 1995	49 F	Breast carcinoma	Generalized persistent pruritic rash and palpable erythematous noduli on the lower legs
3	Routier[5] 1997	60 M	Bronchial carcinoma	Maculopapular eruption
4	Cabane[6] 1998	45 M	Laryngeal carcinoma	Evanescent eruption
5	Cabane[6] 1998	58 F	Myeloproliferative syndrome	Evanescent maculopapular eruption
6	Neishi[7] 2000	45 F	Breast carcinoma	No skin rash
7	Kianzowa[8] 2000	48 F	Breast carcinoma	Evanescent maculopapular eruption
8	Present case	49 F	Breast carcinoma	Erythema multiforme

multiforme, which apparently is not characteristic of AOSD. The rash typically seen in AOSD consists of macular or maculopapular, nonpruritic, small salmon-pink eruptions whose pathology consists of mild perivascular inflammation in the superflcial dermis. It is occasionally urticarial.[13] On the other hand, erythema multiforme is commonly caused by drug allergy, viral infection, and in rare cases neoplasms.

Although AOSD-like manifestations in paraneoplastic syndrome are a rare phenomenon, several cases have been reported elsewhere (Table 1).[3–8] It seems difflcult to differentiate AOSD-like paraneoplasia from AOSD based on the clinical manifestations.

For example, joint involvements were described in all the reported cases, and they were similar to those seen in AOSD. Five of the seven patients had inflammatory arthritis, four of which were of a symmetrical pattern. Affected joints varied among the cases, but relatively large joints were preferentially involved, such as the wrists, elbows, and knees. In the present case, arthritis was seen in the bilateral shoulder joints, which responded quickly to steroid therapy. AOSD-like skin rashes were found in the reported cases except in case 2 and the present case. Interestingly, flve of the eight cases listed in Table 1 were caused by breast carcinoma, and the other three resulted from various malignant disorders. Compared with idiopathic AOSD, paraneoplastic syndrome tends to occur in relatively elderly people. All of the patients reported in the literature were at least 45 years of age at onset, whereas in a nationwide survey of Japanese cases[14] 81% of the 78 patients with idiopathic AOSD were under age 45 years. Apart from the paraneoplastic effects of neoplasms, it is important not to overlook malignant lymphoma, which occasionally exhibits AOSD-like characteristics, including spiking fever, high levels of serum ferritin, and soluble IL-2 receptor.[15]

The mechanism by which neoplasms cause AOSD-like symptoms to develop is unclear, but hypercytokinemia resulting from tumor immunity might play a role in the pathogenesis. On the third hospital day, the serum levels of our patient's inflammatory cytokines were markedly elevated: IL-6 at 370 pg/ml (normal $\leq$ 5.6 pg/ml), interferon-γ at 1020 pg/ml ($\leq$21 pg/ml), and tumor necrosis factor-α at 22.5 pg/ml ($\leq$12 pg/ml). An isolated case of paraneoplastic syndrome caused by breast carcinoma and exhibiting hypercytokinemia has been reported elsewhere.[4] All of these cytokines are known to be elevated in idiopathic AOSD as well.[16,17] The reason only a small portion of the patients with malignancy produce unusually high levels of cytokines remains to be elucidated. Recently, the potential role of another cytokine, IL-18, has been reported in the pathogenesis of AOSD in which there was a correlation between the serum levels of IL-18 and both the ferritin level and the severity of AOSD.[18] However, serum IL-18 has been reported to increase also in patients with breast cancer, esophageal cancer, and hematological malignancies; therefore, measuring the levels of these cytokines is not useful for the differential diagnosis.[19]

The severe anemia seen in the present case could be ascribed to pure red blood cell aplasia (PRCA). Adverse effects of drugs cannot be ruled out, but those that are known to cause PRCA were not administered in this case. Although parvo B19 and cytomegalovirus infections could cause PRCA, neither was suggested by serological tests. Paraneoplastic syndrome might have been one of the causes of PRCA in the present case, as a similar case of breast carcinoma has been reported in the literature.[20] Another possible cause of the anemia is hemophagocytosis. The second bone marrow aspiration, however, showed only red blood cell aplasia, without erythrophagocytosis.

Conclusions

Our case suggests that paraneoplastic syndrome can present manifestations mimicking AOSD. Therefore, a systematic survey of neoplasms should be carried out, especially in a patient more than 45 years of age with AOSD-like manifestations and an atypical skin rash.

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