Brain Metastases of Malignant Melanoma Showing Unbalanced Whole Arm Chromosomal Translocations der (8; 14) (q10; q10) and der (11; 15) (q10; q10) in a Japanese Patient

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Abstract

Since malignant melanoma is a rare malignancy in Japan, little is known about the cytogenetic abnormalities in Japanese patients. We report a case of malignant melanoma showing complex chromosomal abnormalities. A 70-year-old woman was admitted to our hospital because of anorexia, delirium, and right hemiplegia. Cranial CT disclosed several metastatic brain tumors. Multiple subcutaneous and intra-abdominal metastases were also found. A diagnosis of metastatic malignant melanoma was made by biopsy of a subcutaneous tumor. Chromosomal analysis of the tumor cells disclosed complex karyotypic abnormalities including novel unbalanced whole arm translocations der (8; 14) (q10; q10) and der (11; 15) (q10; q10).

(International Medicine 40: 956-960, 2001)

Key words: CT, chromosome analysis, lack of HLA-DR

Introduction

Malignant melanomas originate from melanocytes present normally in the epidermis and sometimes in the dermis. They also develop in the uvea or in the mucous membrane; other primary sites are extremely rare. Melanoma is one of the most common forms of cancer in Western countries and the incidence has increased dramatically. However, malignant melanoma is still rare in Japanese as well as in Blacks and East Asians.

We report a case of malignant melanoma with multiple metastases in a Japanese patient. The patient initially presented with metastatic brain tumors. The primary site of the disease was not discovered by thorough physical examinations. Chromosomal analysis of the tumor cells was available in this case. The value of chromosomal analysis is not well established in human solid tumors as well as in hematological malignancies. Therefore, little is known about the significance of cytogenetic abnormalities of malignant melanoma, especially in Japanese patients. Here, we show the complex chromosome abnormalities including novel whole arm chromosomal translocations der (8; 14) (q10; q10) and der (11; 15) (q10; q10) observed in our patient.

Case Report

A 70-year-old woman was admitted to our hospital in September 2000, because of anorexia, delirium, and right hemiplegia.

The patient had been in good health until a month earlier, when she noticed a small node in her left inguinal area. A week before admission when her brother died of pancreatic cancer, anorexia and increasing weakness developed followed by difficulty in standing. These symptoms were initially considered as a psychosomatic reaction to her brother’s death. As she subsequently developed disorientation and delirium, her sister brought her to our hospital.

On examination, her temperature was 36.2°C, pulse was 59, and the respirations were 16. Her blood pressure was 122/86 mmHg. Motions of the right upper and lower extremities were poor and the right Babinski sign was present. An emergency cranial CT scan was performed, suspecting a cerebral stroke. As shown in Fig. 1, multiple space occupying lesions with high-density areas were found, indicating metastatic brain tumors with intra-tumor bleeding.

The liver and spleen were not palpated. Several subcutaneous tumors in the abdomen, the enlarged left inguinal lymph node, and the enlarged left inguinal lymph node were palpated. An abdominal CT scan disclosed several enlarged intra-abdominal lymph nodes, intra-abdominal tumors, a tumor in the right psoas muscle, and several subcutaneous tumors (Fig. 2).

The patient was a widow and used to be a homemaker. She had worked as a hospital volunteer until a year before admis-
Brain Metastasis of Malignant Melanoma

Figure 1. Cranial CT scan. A high density space occupying lesion (SOL) surrounded by edema in the left parietal lobe (A). Mid-line shift was observed (B, C). A round tumor showing niveau and a small high density tumor in the right occipital lobe were observed (B). A high density tumor with advanced cerebral edema was observed in the left temporal lobe extending to the middle cranial fossa (C, D). A high density tumor in the left hemisphere of cerebellum was observed (D).

A hysterectomy was performed because of a uterus myoma when she was in her thirties. She underwent a sigmoid colectomy and an oophorectomy about 12 years earlier probably because of a malignancy. The precise information was not available.

Laboratory studies showed that the blood count and blood chemistry tests were normal except for the elevated lactate dehydrogenase (1,025 IU/l). The urine was normal. Serum interleukin 2 receptor and D-dimer were slightly elevated at 697 U/ml and 5.75 mg/ml, respectively. The immunochemical fecal occult blood test was positive.

The subcutaneous tumor at the right of the navel was biopsied. As shown in Fig. 3, pigment-laden cells were found among the non-pigmented tumor cells. The cells were positive for S-100 and HMB-45, and negative for EMA or other lymphocyte antigens. Thus, a diagnosis of malignant melanoma was made. No primary melanoma lesions in the entire cutaneous surface, the nails, the oral mucous membrane, the nasal membrane or the eyes were detected.

The patient could not intake any food after the admission and intra-venous nutrition was started. The subcutaneous tumors were visibly enlarged day by day and the weakness progressed. She died on the 36th hospital day.

Flow cytometrical analysis of the biopsied specimen disclosed that the cells lacked any hematological antigens tested (CD2, 3, 4, 5, 7, 8, 14, 16, 19, 20, 34, 38, and 56) as well as HLA-DR antigen. Chromosome analysis of the biopsied specimen was performed (Table 1 and Fig. 4). Numerical abnormalities and several structural abnormalities were observed. Among them, unbalanced whole arm chromosomal transloca-
Figure 2. Contrast enhanced abdominal CT scan. A tumor on the surface of the left lobe of the liver and an enlarged lymph node in the hilus of the spleen (A). Tumors on the surface of the right lobe of the liver and in the hilus of the left kidney (B). A subcutaneous tumor (C). A tumor in the right psoas muscle (D). A lobulated subcutaneous tumor and an enlarged lymph node in the right pelvic cavity (E). An enlarged inguinal lymph node (F).

Figure 3. Histopathology of a biopsied specimen. Pigmented melanoma cells were seen among non-pigmented melanoma cells. HE stain, ×200 (A). HE stain, ×400 (B).
### Table 1. Karyotype Analysis of Biopsied Specimen

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<th>Karyotype Analysis</th>
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<tr>
<td>40, X, −X, add (1) (q12), −4, −5, +add (6) (q13), add (6) (q13), der (8; 14) (q10; q10), −10, add (10) (q26), der (11; 15) (q10; q10), add (12) (q24.3), add (13) (p11), −21, −22, −22, +2mar</td>
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<tr>
<td>41, X, −X, add (1) (q12), −4, −5, +add (6) (q13), add (6) (q13), der (8; 14) (q10; q10), −10, add (10) (q26), der (11; 15) (q10; q10), add (12) (q24.3), add (13) (p11), −19, −21, −22, −22, +4mar</td>
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<td>80, XX, −X, −X, add (1) (q12) x2, −4, −4, −5, −5, +add (6) (13), add (6) (q13) x2, der (8; 14) (q10; q10) x2, −10, −10, add (10) (q26) x2, der (11; 15) (q10; q10) x2, add (12) (q24.3) x2, add (13) (p11) x2, −16, −17, −20, −21, −22, −22, −22, −22, +8mar</td>
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**Figure 4.** Chromosome analysis. 40, X, −X, add (1) (q12), −4, −5, +add (6) (q13), add (6) (q13), der (8; 14) (q10; q10), −10, add (10) (q26), der (11; 15) (q10; q10), add (12) (q24.3), add (13) (p11), −14, −15, −21, −22, −22, +2mar.
not only the numerical but structural chromosome anomalies. Thompson et al reported that the most common clonal numerical abnormalities and clinical outcome in metastatic melanoma (3). Patients with structural abnormalities of chromosome 7 or 11 had a significantly shorter survival than patients without these abnormalities. Indeed, the structural abnormality of chromosome 11 was also observed in the present case. Cytogenetic analysis may provide useful prognostic information about patients with metastatic melanoma.

Thompson et al reported that the most common clonal numerical abnormalities were -10, -22, -9, +7, -19, and -Y in a cytogenetic study of 158 patients with regional or disseminated melanoma (4). The present case disclosed homozygous allelic loss of chromosome 22 in all the cells analyzed, however -19 was detected in only one cell analyzed. They also suggested the importance of structural abnormalities of chromosome 1, 6, and 10 in the pathogenesis of sporadic advanced melanoma. Interestingly, our case had structural abnormalities of chromosome 1, 6, and 10 as add (1) (q12), add (6) (q13), and add (10) (q26), respectively.

Germ-line mutations in the CDKN2A tumor-suppressor gene have been linked to not only to familial melanomas but to sporadic melanomas (5). Since the gene located on 9p21, allelic losses of 9p may correlate with functional loss of the CDKN2A. However, our case showed no deletions of chromosome 9. Deletions of chromosome 4, 5, 10, 21, and 22 were consistently observed in our case.

Not only the numerical but structural chromosome abnormalities were observed in our case. Among them, unbalanced whole arm translocations der (8; 14) (q10; q10) and der (11; 15) (q10; q10) were present in all the cells analyzed.

**Discussion**

Our patient initially presented with metastatic brain tumors of unknown origin. The examinations disclosed that the patient had multiple metastases of malignant melanoma, however the primary site was not discovered. Although malignant melanoma most commonly arises in the skin, primary melanomas can also arise from the mucosal epithelial lining of the gastrointestinal tract (1). The primary site might have been the gastrointestinal tract in the present case since the fecal occult blood test was positive. However, the patient’s condition did not allow us to perform gastrointestinal endoscopic examinations.

Brain metastases are a common and devastating complication in patients with malignant melanoma. Therapeutic options for these patients are limited, and the prognosis is usually poor. A retrospective review of 6953 patients with melanoma treated at a single institution showed clinically significant brain metastases in 702 of these patients (2). The overall median survival time of all patients with brain metastases was 113.2 days.

Complex karyotype anomalies were observed (Table 1 and Fig. 4), suggesting the existence of chromosome instability in our case. Trent et al reported on the relation between cytogenetic abnormalities and clinical outcome in metastatic melanoma (3). The most common clonal numerical abnormalities were -10, -22, -9, +7, -19, and -Y in a cytogenetic study of 158 patients with regional or disseminated melanoma (4). The present case disclosed homozygous allelic loss of chromosome 22 in all the cells analyzed, however -19 was detected in only one cell analyzed. They also suggested the importance of structural abnormalities of chromosome 1, 6, and 10 in the pathogenesis of sporadic advanced melanoma.

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Not only the numerical but structural chromosome abnormalities were observed in our case. Among them, unbalanced whole arm translocations der (8; 14) (q10; q10) and der (11; 15) (q10; q10) were notable. Whole arm translocations are events in which breakpoints occur in the centromeric regions (6). The centromere to centromere translocations between long arms of chromosomes 8 and 14, and between long arms of chromosomes 11 and 15 occurred in our case. Unbalanced whole arm translocations are observed in a special case that may result in the loss of one or two entire chromosome arms. Indeed, the short arms of chromosomes 8, 14, 11, and 15 were lost in our case. To our knowledge, these der (8; 14) (q10; q10) and der (11; 15) (q10; q10) have never been reported in melanomas or other malignancies (3, 4, 7). However, the significance of these translocations in the pathogenesis of melanomas remains to be investigated.

It should be noted that the tumor cells lacked HLA-DR antigen in the present case. The majority of melanomas express HLA-DR antigens (8), while no HLA-DR antigens are expressed on normal melanocytes (9). We and others reported the induction CD4+ cytotoxic T lymphocytes specifically-lysed autologous melanoma cells in the context of HLA-DR (10, 11). Loss of HLA-DR antigens on melanoma cells may result in the escape from immune-surveillance from such CD4+ T cells. The absence of HLA-DR antigens on melanoma cells might partly explain the devastating clinical course in our patient.

**References**