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Leukemia in cardio-facio-cutaneous (CFC) syndrome: A patient with a germline mutation in BRAF proto-oncogene

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Abstract: Cardio-facio-cutaneous (CFC) syndrome is a multiple congenital anomaly/mental retardation syndrome characterized by a distinctive facial appearance, ectodermal abnormalities and heart defects. Clinically, it overlaps with both Noonan syndrome and Costello syndrome, which are caused by mutations in two genes that encode molecules of the RAS/MAPK (mitogen activated protein kinase) pathway (PTPN11 and HRAS, respectively). Recently, mutations in KRAS, BRAF and MEK1/2 have been identified in patients with CFC syndrome. Somatic mutations in KRAS and BRAF have been identified in various tumors. In contrast, the association with malignancy has not been noticed in CFC syndrome. Here we report a 9-year-old boy diagnosed with CFC syndrome and acute lymphoblastic leukemia. Sequencing analysis of the entire coding region of KRAS and BRAF showed a de novo germline BRAF E501G (1502A→G) mutation. Molecular diagnosis and careful observations should be considered in children with CFC syndrome because they have germline mutations in proto-oncogenes and might develop malignancy.

This piece of the submission is being sent via mail.

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December 21, 2006

Dr. Kjeld Schmiegelow
Associate Editors
Journal of Pediatric Hematology and Oncology

Re: JPHO 06-168 Leukemia in cardio-facio-cutaneous (CFC) syndrome: a patient with a germline mutation in BRAF proto-oncogene

Dear Dr. Kjeld Schmiegelow,

Thank you for your E-mail on November 30, 2006, regarding our manuscript referenced above. We thank the reviewer's for their insightful comments. The manuscript was revised according to the reviewer's suggestions. The revised sentences were indicated by red.

I must tell you that our manuscript regarding mutation analysis of 54 CFC patients has been in press in the American Journal of Medical Genetics (submitted on July 12, 2006 and accepted on November 18). The information of the patient in the revised manuscript is also included in the AJMG manuscript as one of the 54 CFC patients, but detailed clinical manifestations are not described. The manuscript (ref 10) is cited in the text.

We hope that the revised manuscript is now acceptable for publication. Thank you for your kind consideration of our manuscript.

Sincerely yours,

Yoko Aoki MD. PhD

Reviewer #1: General comments: The manuscript describes the second patient ever described with cardio-facio-cutaneous (CFC) syndrome to develop a malignancy. The paper is well written although there are a number of areas of clarification that are required as listed in the specific comments.

Specific comments are as follows:

Introduction:

1. Page 3, Paragraph 2, and line 4 - The authors state that mutations of KRAS and BRAF "were identified in various tumors." Please give details regarding which tumors were identified and supply appropriate references.

As the reviewer suggested, we gave details regarding tumors identified and supplied references.

Case report:

1. Page 4, paragraph 2 - Please clarify that no testicular biopsy was performed to confirm diagnosis of testicular involvement. Also please supply a reference on how computed tomography is a validated evaluation for confirmation of testicular involvement.

We carefully checked the medical record of the patient again and found that testicular biopsy of the right testis was performed to confirm testicular involvement. We revised the sentence as follows, "Testicular involvement was confirmed by testicular biopsy".

2. Cytogenetics results - please state the actual results of the karyotype including how many metaphases were evaluated.

As the reviewer suggested, we added how many metaphases were evaluated. "Cytogenetic analysis of bone marrow aspiration was 46, XY (20 cells counts)"

3. Molecular evaluation of the ALL blasts appears to have been done as inferred in table 1 for TEL/AML1. Please list the molecular evaluations for TEL/AML1, MLL rearrangements, BCR/ABL if they were performed and that they were in fact not present.

We only performed conventional cytogenetic analysis. No visible translocation was detected.

4. Were there any analyses for the presence of ALL at birth performed on blood obtained in Guthrie spots or their equivalent? If such data were available, it would enhance the paper.

The reviewer's suggestion is interesting. Unfortunately, we are not allowed to use retrospective studies on disease conditions other than specified diseases in Japan.

Discussion:

1. Page 6, paragraph 1 - There is a reference that "somatic mutations in BRAF have been identified in 7% of cancer." Please supply more detail about the types of cancer and their relative frequency.

As the reviewer suggested, we supplied the details of cancer with BRAF mutations and their relative frequency.

Tables

1. Table 1 - please add in the results of the karyotypes of patients 1 and 2. Also be more specific regarding the translocations evaluated and the results.

As the reviewer suggested, we added the results of the karyotypes of patients 1 and 2 and translocations in Table 1.

Leukemia in cardio-facio-cutaneous (CFC) syndrome: a patient with a germline mutation in BRAF proto-oncogene

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Key words: cardio-facio-cutaneous syndrome, KRAS, BRAF, RAS/MAPK, leukemia

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Summary: Cardio-facio-cutaneous (CFC) syndrome is a multiple congenital anomaly/mental retardation syndrome characterized by a distinctive facial appearance, ectodermal abnormalities and heart defects. Clinically, it overlaps with both Noonan syndrome and Costello syndrome, which are caused by mutations in two genes that encode molecules of the RAS/MAPK (mitogen activated protein kinase) pathway (*PTPN11* and *HRAS*, respectively). Recently, mutations in *KRAS*, *BRAF* and *MEK1/2* have been identified in patients with CFC syndrome. Somatic mutations in *KRAS* and *BRAF* have been identified in various tumors. In contrast, the association with malignancy has not been noticed in CFC syndrome. Here we report a 9-year-old boy diagnosed with CFC syndrome and acute lymphoblastic leukemia. Sequencing analysis of the entire coding region of *KRAS* and *BRAF* showed a *de novo* germline *BRAF* E501G (1502A→G) mutation. Molecular diagnosis and careful observations should be considered in children with CFC syndrome because they have germline mutations in proto-oncogenes and might develop malignancy.

Cardio-facio-cutaneous (CFC) syndrome is a multiple congenital anomaly/ mental retardation syndrome characterized by heart defects, facial dysmorphism, ectodermal abnormalities and mental retardation.^{1,2} CFC syndrome has many clinical features in common with those with Noonan syndrome and Costello syndrome, which are caused by mutations of proto-oncogenes *PTPN11* and *HRAS*, respectively. Both genes encode molecules in the RAS/mitogen activated protein kinase (MAPK) signaling pathway.^{3,4} It has been reported that patients with Noonan syndrome develop juvenile myelomonocytic leukemia (JMML), neuroblastoma and rhabdomyosarcoma.⁵ Predisposition to tumors, including neuroblastoma, rhabdomyosarcoma and bladder carcinoma, has been reported in patients with Costello syndrome.⁶ Tumor screening protocols have been proposed for these two syndromes.⁶ In contrast, little attention has been paid for development of tumors in patients with CFC syndrome.

Recently, we and others have identified germline mutations in *KRAS*, *BRAF* and *MEK1/2* in individuals with CFC syndrome.^{2,7} These genes encode molecules in the RAS-RAF-ERK pathway. **Somatic mutations in *KRAS* and *BRAF* were identified in various tumors. *KRAS* mutations occurred frequently in lung, colon and pancreatic cancer⁸ and *BRAF* mutations have been frequently identified in malignant melanoma, colon cancer and thyroid cancer⁹.**

We herewith report a 9-year-old Japanese patient with CFC syndrome associated with acute lymphoblastic leukemia (ALL) in whom a *BRAF* mutation was identified. Our observations, together with literature reviews of previous cases, suggest the importance of careful observation for malignancy in CFC syndrome.

CASE REPORT

The propositus was a 9-year-old Japanese boy. He was the first son of unrelated healthy parents. At birth paternal age was 33 years and maternal age was 22 years. Delivery at

36 weeks was uncomplicated and birth weight of the patient was 3,240 g (+1.8 SD), length 48.7 cm (+0.8 SD), and OFC 39.2 cm (+3.9 SD). At the age of 3 months, the following anomalies were noted (Fig. 1): sparse curly hair, macrocephaly, bitemporal constriction, hyperterolism, downslanting palpebral fissures, low nasal bridge, low set and posterior rotated ears, bilateral cryptorchidism, generalized cutaneous pigmentation and patchy hyperkeratosis, especially on extensor surfaces of limbs. Cardiac features included patent ductus arteriosus (naturally closed). At the age of one year and three months, asymmetrical hypertrophy of the interventricular septum directed towards the apex was noted. Based on the observed facial dysmorphisms, cardiac anomalies and skin abnormalities, he was diagnosed as having CFC syndrome.

He was diagnosed as having ALL at one year and nine months of age, when his weight was 13.0 kg (+1.5 SD), his height was 88.0 cm (+1.3 SD) and his head circumference was 53 cm (+3.3 SD). He showed hepatosplenomegaly and right testicular swelling. **Testicular involvement was confirmed by testicular biopsy.** Lymphoblasts were seen in the peripheral blood (100% of $8.3 \times 10^{10}/l$ leucocytes). Bone marrow aspirate showed 98% lymphoblasts positive for TdT, HLA-DR, CD19, CD10, CD22 and CD79a and negative for cytoplasmic IgM and membranous IgM, CD33, CD34, CD15, CD65, myeloperoxidase and T cell markers. **Cytogenetic analysis of bone marrow aspiration was 46, XY (20 cells counts).** The examination of cerebrospinal fluid showed no lymphoblasts.

Induction therapy, which consisted of vincristine, predonisolone, doxorubicin and E. coli asparaginase, was performed. Remission was achieved in seven weeks. High-dose methotrexate and intrathecal therapy were performed for central nervous system prophylaxis. After induction treatment, right orchidectomy was also performed. During maintenance therapy using vincristine, dexamethasone, 6-mercaptopurine, and methotrexate, a central nervous system relapse was observed at the age of three years and nine months. Systemic investigation, including bone marrow aspiration, showed

isolated central nervous system relapse. He received central nervous system irradiation (whole brain 24 Gy and whole spine 15 Gy, respectively). The maintenance therapy was finished at the age of five years and nine months. Now, at the age of nine years and three months, he is healthy except for severe mental retardation.

Mutation analysis

Genomic DNA from blood leukocytes from the patient and the parents was isolated by a standard protocol. Five coding exons in *KRAS* and 18 coding exons in *BRAF* with flanked introns were amplified by polymerase chain reaction (PCR).^{2, 10} The PCR products were gel-purified and sequenced on an ABI PRISM 310 automated DNA sequencer (Applied Biosystems). This study was approved by the Ethics Committee of Tohoku University School of Medicine. We obtained informed consent for samples and specific consent for a photograph. Sequencing analysis of *BRAF* showed an A→G change at nucleotide 1502, resulting in a E501G mutation, in the heterozygous form¹⁰ (Fig.1b). The E501G mutation was not identified in DNA samples from his parents, suggesting that this mutation occurred *de novo*. No mutations were found in *KRAS*.

DISCUSSION

Germline mutations in *BRAF* have been found to account for 52% of patients with CFC syndrome^{2,7}. A previous report has shown that a patient with CFC syndrome developed ALL at five years of age.¹¹ Later, a *BRAF* G469E mutation was identified in that patient (Table 1)² The type of leukemia was ALL of common phenotype. Chromosomal findings including TEL/AML1 fusion indicate a favorable ultimate outcome.¹¹ In the current study, we identified a *de novo* E501G mutation of *BRAF* in a CFC patient who developed ALL at one year and nine months of age. Chromosomal abnormality of leukemia cells was not observed in the patient. Despite a central nervous system relapse and invasion of the testis by leukemia cells, induction and maintenance therapies were successful. *BRAF* is a proto-oncogene and somatic mutations in *BRAF*

have been identified in 7% of cancer.⁹ *BRAF* has been mutated in approximately 27-70 % in malignant melanoma, 5-22 % of the cases in colon cancer and 36-53 % of thyroid cancer.⁹ The V600E mutation was frequently identified in these cancers. Somatic *BRAF* mutations have been also reported in thirteen hematopoietic or lymphopoietic malignancies (The Sanger Institute Catalogue of Somatic Mutations in Cancer website). Careful observation and molecular analysis of patients can help clarify the predisposition to malignancy in CFC syndrome.

CFC syndrome shares clinical manifestations with Noonan syndrome and Costello syndrome. The clinical data of 19 mutation-positive CFC individuals showed a high frequency of growth failure (78.9%), mental retardation (100%), relative macrocephaly (78.9%), characteristic facial appearance including bitemporal constriction (84.2%) and downslanting palpebral fissures (94.7%), curly sparse hair (100%), heart defects (84.2%) and skin abnormalities (68.4%).² In contrast, Noonan syndrome has lower frequencies of mental retardation (24-35%), heart defects (50-67%) and skin abnormalities (2-27%).¹² Redundant skin (especially in the neck, hands and feet), hypermobility of the small joints (especially in the fingers) and tightness of the Achilles tendons might be important clinical features to diagnose Costello syndrome.⁴

The risk of malignancy and types of tumors developed are different between these syndromes (Table 2). Past studies have shown that patients with Noonan syndrome develop leukemia, including JMML, neuroblastoma or rhabdomyosarcoma.⁵ Patients with Costello syndrome have been reported to develop various tumors, including rhabdomyosarcoma or neuroblastoma in the early infantile period and bladder carcinoma after ten years of age.⁶ Tumor frequency in Costello syndrome has been estimated to be as high as 17% and tumor screening protocol has been proposed.⁶ The association with ALL was reported in two CFC patients with *BRAF* mutations including this report. Molecular diagnosis will lead to correct diagnosis of patients who are suspected of

having Noonan-related syndromes and will be useful to determine the screening plan for malignancy in patients.

URL. The Sanger Institute Catalogue of Somatic Mutations in Cancer website is at <http://www.sanger.ac.uk/cosmic>.

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Figure Legend

Figure 1 (a) Facial appearance of the patient. (b) The *BRAF* mutation in the patient, but not in his parents. The position of the nucleotide substitution is indicated by arrows.

a

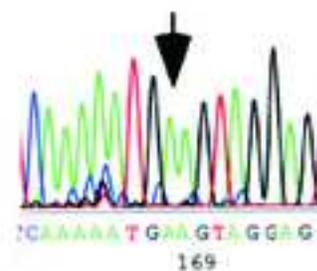


b

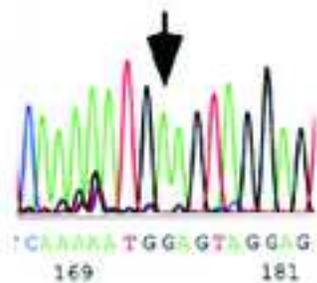
E501G
(1502A→G)

C A A A A A T G A A G T A G G G G
169 181

father



mother



patient

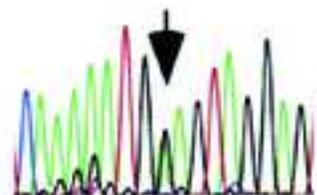


Table 1. Clinical findings in CFC patients who developed ALL

| | Case 1¹¹ | Case 2 (present case) |
|--------------------------------------|--|--|
| Gene | <i>BRAF</i> | <i>BRAF</i> |
| Amino acid change | G469E | E501G |
| CFC | | |
| Facial appearance | typical | typical |
| Heart defects | mild PS, ASD and asymmetrical hypertrophy of the interventricular septum | patent ductus arteriosus and asymmetrical hypertrophy of the interventricular septum |
| Skin | keratosis pilaris (3 y) cafe-au-lait spots | generalized pigmentation and patchy hyperkeratosis |
| Other | | bilateral cryptorchidism |
| ALL | | |
| Age at diagnosis | 5 y | 1 y 9 mo |
| Lymphoblasts in the peripheral blood | 8% of 1.4×10^9 /l leukocytes | 100% of 8.3×10^{10} /l leukocytes |
| Lymphoblasts in bone marrow | 98% lymphoblasts positive for TdT, HLA-DR, CD34, CD13, CD33, CD19, CD10, CD22 and CD79 | 98% lymphoblasts positive for TdT, HLA-DR, CD19, CD10, CD22 and CD79 |
| Chromosomal abnormalities | 45-46, XX, add(3)(p14), del(9)(p21p22), +10,t(12;21)(p13;22), +del(12)(p11;p12), del(15)(q13q24), der(16;19)(q10;p10), del(22)(q11q13)[27] and 46,XX[13] FISH studies were negative for BCR/ABL fusion and positive for TEL/AML1 fusion | 46, XY. No visible structural anomaly was observed. |
| Induction therapy | vincristine, dexamethasone and E.coli asparaginase | vincristine, predonolone, E.coli asparaginase and doxorubicin |
| Central nervous system prophylaxis | methotrexate | methotrexate |
| Maintenance therapy | vincristine, dexamethasone, 6-MP and methotrexate | vincristine, dexamethasone, 6-MP and methotrexate |
| Central nervous system relapse | absent | present (during maintenance therapy) |
| Outcome | unknown | healthy as of age 9 y 3 mo |
| Other | | testicular involvement |

Table 2. Noonan, Costello and CFC syndromes and associated tumors

| Disease | Cancer | References |
|-------------------|-----------------------------------|-------------------|
| Noonan syndrome | rhabdomyosarcoma | 13, 14 |
| | subcutaneous granular-cell tumors | 15 |
| | neuroblastoma | 16-18 |
| | juvenile myelomonocytic leukemia | 19-24 |
| | myeloproliferative disorder | 24-27 |
| | acute lymphoblastic leukemia | 28 |
| Costello syndrome | rhabdomyosarcoma | 4, 6, 29-31 |
| | neuroblastoma | 4, 32 |
| | bladder carcinoma | 33, 34 |
| CFC syndrome | acute lymphoblastic leukemia | 11, this study |
| | rhabdomyosarcoma | 35 |