FUS-ERG gene fusion in isolated myeloid sarcoma showing uncommon clinical features

Ryosuke Ueda¹, Dai Maruyama¹*, Junko Nomoto¹, Akiko M. Maeshima², Suguru Fukuhara¹, Hideaki Kitahara¹, Ken-ichi Miyamoto⁴, Wataru Munakata¹, Tatsuya Suzuki¹, Hirokazu Taniguchi², Yukio Kobayashi¹, and Kensei Tobinai¹

¹Department of Hematology, National Cancer Center Hospital, Tokyo, Japan and ²Department of Pathology and Clinical Laboratory, National Cancer Center Hospital, Tokyo, Japan

*Correspondence address. Department of Hematology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81-3-3542-2511; Fax: +81-3-3542-3815; E-mail: dmaruyam@ncc.go.jp

Abstract

FUS-ERG gene fusion has not been reported in cases of myeloid sarcoma (MS), a subtype of acute myeloid leukemia involving extramedullary anatomic sites. Here, we report a case of a 48-year-old man with primary isolated MS of the anterior mediastinum, who later developed multiple extramedullary recurrences without bone marrow infiltration throughout the course. G-banding analysis of the cells in pericardial effusion at recurrence showed complex karyotypic abnormalities including t(16;21)(p11.2;q22). FUS break-apart fluorescent in situ hybridization analysis showed split signals in biopsy sections at initial diagnosis and recurrence. Reverse transcriptase polymerase chain reaction and direct sequencing demonstrated the presence of the FUS-ERG chimeric gene transcript. The patient underwent cord blood transplantation, but died of pneumonia on day 64. To our knowledge, this is the first report of isolated MS carrying FUS-ERG gene fusion. In future study, relationship between the fusion gene and uncommon clinical features should be investigated in isolated MS.

INTRODUCTION

FUS-ERG gene fusion can be detected in patients with acute myeloid leukemia (AML) and has been reported to be associated with poor prognosis [1]. Myeloid sarcoma (MS) is a subtype of AML involving extramedullary anatomic sites. MS usually arises in patients with AML involving bone marrow (BM) both at first presentation and in the clinical course. Here, we report a patient with primary isolated MS of the anterior mediastinum, who had FUS-ERG gene fusion and later developed multiple extramedullary recurrences without BM infiltration throughout the course.

CASE REPORT

A 48-year-old man was referred to our hospital because of a supraclavicular mass. He had been well until 3 months before admission, when he had developed cough and noticed the mass. He had a history of pulmonary emphysema. Fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomography (CT) showed increased FDG uptake in the supraclavicular lymph nodes, and a bulky anterior mediastinal tumor (Fig. 1A–C). Fine needle biopsy from the mediastinal tumor was performed. Hematoxylin and eosin-stained mediastinal sections showed diffuse infiltration of medium-sized tumor cells (Fig. 1F...
and G). Immunohistochemistry demonstrated that the tumor cells were negative for CD1a, CD3, CD8, CD20 and TdT, and positive for CD4, CD43, CD56 (Fig. 1H) and CD99 (Fig. 1I). BM examination revealed no evidence of the infiltration of tumor cells throughout the course. The patient was diagnosed as having T-lymphoblastic lymphoma of clinical stage IIA and underwent an acute lymphoblastic leukemia-type chemotherapy regimen [2]. After the induction chemotherapy, he achieved partial response, and received subsequent post-remission and central nervous system prophylaxis therapies according to the treatment schedule. He also underwent 30 gray (Gy)/15 fraction (Fr) radiation therapy (RT) for the mediastinal bulky mass according to the treatment schedule. However, marginal relapse of the irradiated field was detected during the post-remission therapy. He underwent an additional 36 Gy/18 Fr RT for the lesion that progressively increased in size.

Figure 1: FDG-PET/CT showed remarkable FDG uptake in anterior mediastinum (A–C). CT revealed right testicular swelling (D). Head MRI showed multiple parenchymal invasions (E). Mediastinal sections at low (F) and high (G) magnifications showed diffuse infiltration of medium-sized tumor cells with scant cytoplasm and dense chromatin, which was accompanied by nuclear fragmentation. The tumor cells were positive for CD56 (H) and CD99 (I). Testicular mass sections at relapse showed diffuse stromal infiltration of medium- to large-sized atypical cells with no apparent differentiation to neutrophils or monocytes (J and K). The tumor cells were positive for MPO (L) and CD34 (M).
Because he noticed painless right testicular swelling 10 months after the start of treatment, right orchiectomy was performed for diagnosis (Fig. 1D). Histopathologically, slides of testicular mass sections showed diffuse stromal infiltration of medium- to large-sized atypical cells (Fig. 1J and K). Immunohistochemical analysis revealed that the tumor cells were negative for CD3, CD20, CD68 (PGM1) and TdT, and positive for CD4, CD56, MPO (Fig. 1L) and CD34 (Fig. 1M). Initial slides of mediastinal sections were retrospectively examined and positivity for MPO was confirmed. The tumor was diagnosed as MS. Although he had no neurological symptoms, cerebrospinal fluid examination showed infiltration of myeloid blasts. We started high-dose

Figure 2: Break-apart FISH analysis revealed FUS gene rearrangement in paraffin-embedded tumor sections both at first presentation (A) and at recurrence (B). RNA was extracted from patient’s frozen tissue, YNH-1 cultured cells (from RIKEN Cell Bank, Tsukuba, Japan) as a positive control, and K562 cultured cells as a negative control. RT-PCR analysis of FUS-ERG fusion gene transcripts was performed, and agarose gel electrophoresis showed one major band of 191 bp (Type B) and one minor band of 230 bp (Type A) in the patient (Lane 1) and YNH-1 cells (Lane 2) (C). Sequence of chimeric transcripts showed that exon 7 of the FUS gene located at 16p11 was fused in frame to exon 12 of the ERG gene located at 21q22 (D).
cytarabine (HDAC) therapy. However, the patient gradually developed headache, and head magnetic resonance imaging (MRI) detected multiple intraparenchymal masses, which were considered as the invasion of MS (Fig. 1E). He underwent 30 Gy/10 Fr whole-brain RT. We also started intrathecal (IT) injection of cytarabine, and blasts in cerebrospinal fluid were decreased.

After a total of three courses of HDAC therapy and IT cytarabine therapy, he achieved first complete remission (CR). However, he developed acute renal failure and abdominal CT showed hydrenephrosis due to retroperitoneal mass. Needle biopsy from the retroperitoneal mass revealed recurrence of MS. In addition, pleural and pericardial effusions developed, and G-banding analysis of the cells in pericardial effusion showed an abnormal karyotype of 47,XY,add(2)(q13.1),del(9)(q?),+10,t(16;21)(p11.2;q22), add(17)(p11.2),+17,add(2)[5,15],idem,add(2)[p13][5]. FUS gene break-apart fluorescent in situ hybridization (FISH) analysis showed split signals in biopsy sections of the mediastinum at initial diagnosis and the tests at recurrence (Fig. 2A and B). Reverse transcriptase polymerase chain reaction (RT-PCR) and direct sequence analysis demonstrated the presence of the FUS-ERG chimeric gene transcript (Fig. 2C and D) [3]. As described previously [1], the outer primer set of 4F1-8R was used in first PCR, and the inner primer set of FUS1-ERG3 was used in second PCR and direct sequencing. The sequences of the PCR primers used were as follows: 4F1, 5′-CTAT

In conclusion, we report for the first time primary isolated MS with FUS-ERG gene fusion. In future study, it should be investigated whether a causal relationship exists between the fusion gene and uncommon clinical features in isolated MS.

ETHICAL APPROVAL AND CONSENT

No ethical approval is required for case reports in our institution. The research was conducted in accordance with the Helsinki Declaration. The submission of a case report was approved by the patient and relatives. However, the patient was already deceased and the relatives cannot be traced. Therefore, it is difficult to obtain consent once more now. Furthermore, this work is anonymized as much as possible. Dai Maruyama, MD, PhD is a guarantor of this study.

FUNDING

This work was supported in part by the National Cancer Center Research and Development Fund (26-A-4, 26-A-24), a grant for cancer research (Practical Research for Innovative Cancer Control) from the Japan Agency for Medical Research and Development (AMED) and a grant-in-aid for Scientific Research (C 25461442).

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Kong XT, Ida K, Ichikawa H, Shimizu K, Ohki M, Maseki N, et al. Consistent detection of TLS/FUS-ERG chimeric transcripts in acute myeloid leukemia with t(16;21)(p11;q22) and identification of a novel transcript. Blood 1997;90:1192–9.
2. Azuma T, Tobinai K, Takeyama K, Shibata T, Hidaka M, Kurosawa M, et al. Establishment of a novel human acute myeloid leukemia cell line (YNH-1) with t(16;21), t(1;16), and 12q21, 1q12 and 20q11 translocations. Leukemia 1997;11:599–608.
3. Yamamoto K, Otsuka H, Nagata K, Kobayashi M, Tanimoto F, Taniiwaki M. Establishment of a novel human acute promyelocytic leukemia cell line (YNH-1) with t(16;21), t(1;16) and 12q13, 1q12 and 20q11 translocations. Leukemia 1997;11:599–608.
4. Byrd JC, Edfeldt WJ, Shields DJ, Dawson NA. Extramedullary myeloid cell tumors in acute nonlymphocytic leukemia: a clinical review. J Clin Oncol 1995;13:1800–16.
5. Wong WS, Loong F, Ooi GC, Tse TC, Chim CS. Primary granulocytic sarcoma of the mediastinum. *Leuk Lymphoma* 2004; 45:1931–3.
6. Mi Lee J, Song H-N, Kang Y, Kim H, Hyun Min J, Sun Suh Y, et al. Isolated mediastinal myeloid sarcoma successfully treated with chemoradiotherapy followed by unrelated allogeneic stem cell transplantation. *Intern Med* 2011;50:3003–7.
7. Neiman RS, Barcos M, Berard C, Bonner H, Mann R, Rydell RE, et al. Granulocytic sarcoma: a clinicopathologic study of 61 biopsied cases. *Cancer* 1981;48:1426–37.
8. Pileri SA, Ascani S, Cox MC, Campidelli C, Bacci F, Piccioli M, et al. Myeloid sarcoma: clinicopathologic, phenotypic and cytogenetic analysis of 92 adult patients. *Leukemia* 2007;21:340–50.
9. Chen D, Bachanova V, Ketterling RP, Begna KH, Hanson CA, Viswanatha DS. A case of nonleukemic myeloid sarcoma with FIP1L1-PDGFRA rearrangement: an unusual presentation of a rare disease. *Am J Surg Pathol* 2013;37:147–51.
10. Bakst RL, Tallman MS, Douer D, Yahalom J. How I treat extramedullary acute myeloid leukemia. *Blood* 2011;118:3785–93.