OMCR

Oxford Medical Case Reports, 2016; 1, 4–8

doi: 10.1093/omcr/omv070
Case Report

CASE REPORT

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

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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

Received: October 29, 2015. **Revised:** November 15, 2015. **Accepted:** December 1, 2015

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.

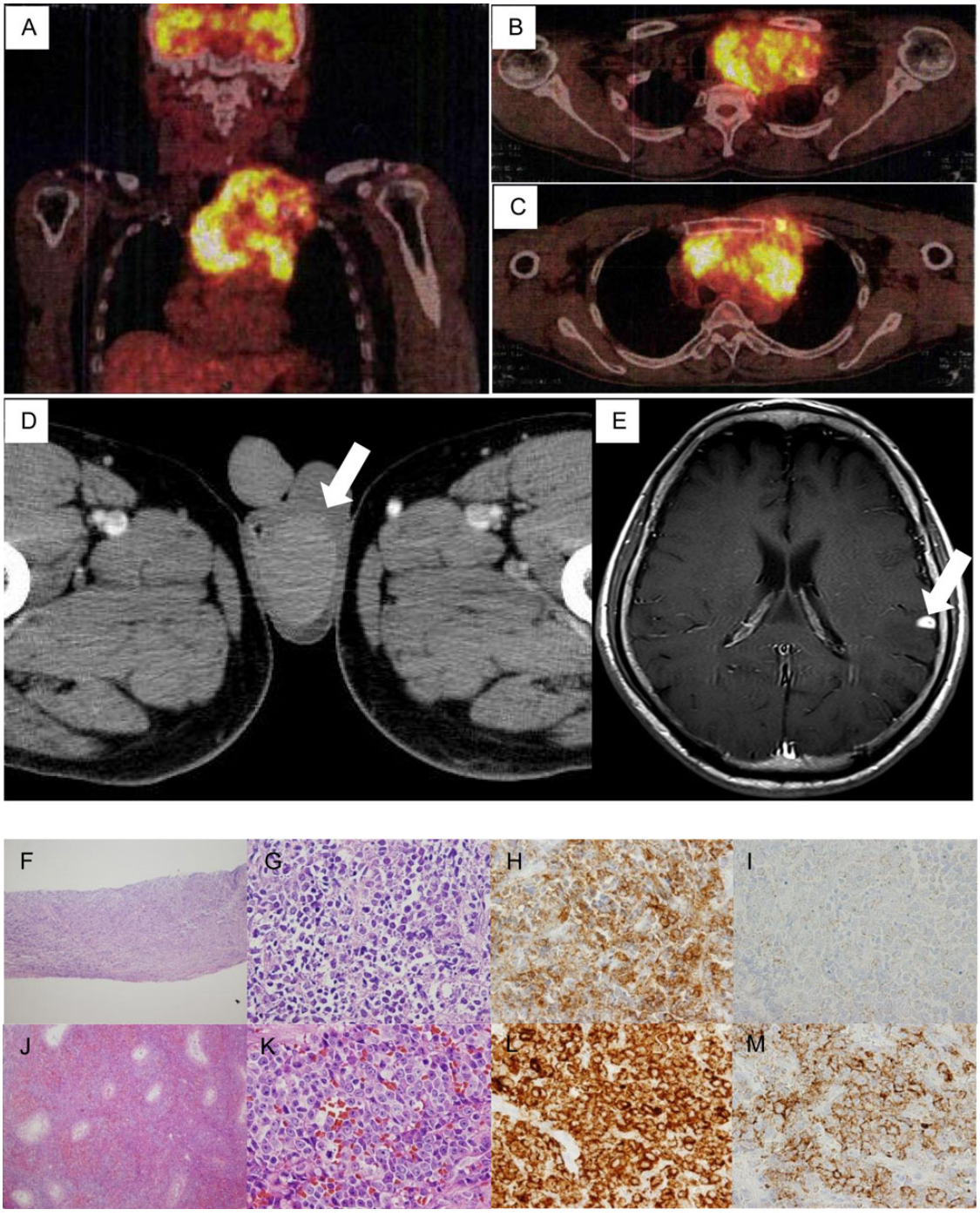

Figure 1: FDG-PET/CT showed remarkable FDG uptake in anterior mediastinum (**A–C**). CT revealed right testicular swelling (**D**). Head MRI showed multiple parenchymal invasions (**E**). Mediastinal sections at low (**F**) and high (**G**) magnifications showed diffuse infiltration of medium-sized tumor 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

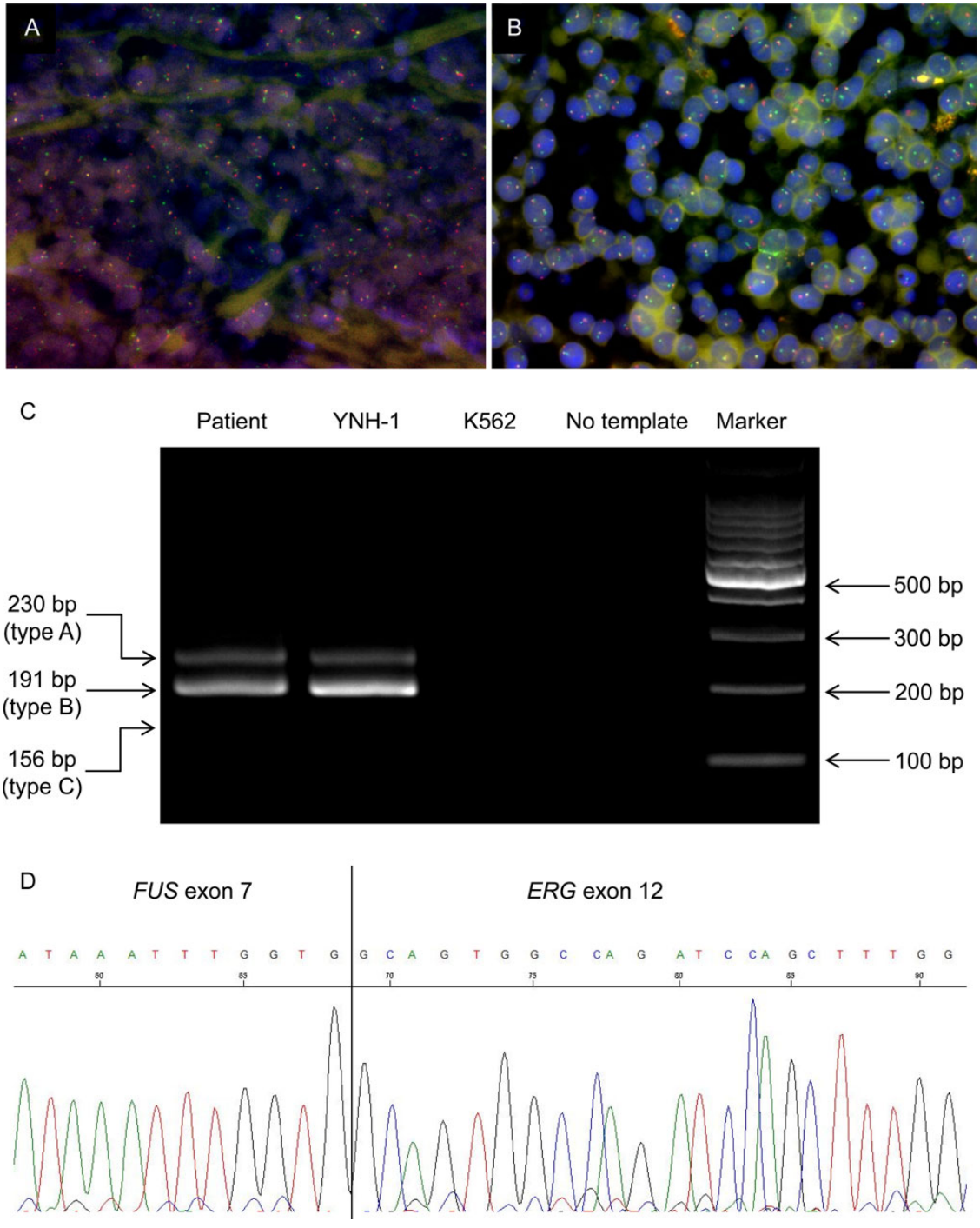

Figure 2: Break-apart FISH analysis revealed *FUS* gene rearrangement in paraffin-embedded tumor sections both at first presentation (**A**) and at recurrence (**B**). RNA was extracted from patient's frozen tissue, YNH-1 cultured cells (from RIKEN Cell Bank, Tsukuba, Japan) as a positive control, and 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 hydronephrosis 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)(q21),del(9)(q?),+10,t(16;21)(p11.2;q22),add(17)(p11.2)[15]/47,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 testis 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′-CTATGGACAGCAGGACCGTG-3′; 8R, 5′-CATAGTAGTAACGGAGGGCG-3′; FUS 1, 5′-GGTGGCTATGAACCCAGAGG-3′; and ERG 3, 5′-TTGAACTCCCCGTTGGTGCC-3′. Furthermore, upper gastrointestinal endoscopy showed a gastric mass, which was thought to be MS invasion.

The patient received salvage chemotherapy and subsequently underwent cord blood transplantation in non-CR, but died of severe pneumonia on day 64. Autopsy was performed, and unexpectedly, we found a residual MS lesion only in the left testis, despite the aggressive clinical course.

DISCUSSION

Primary isolated MS is very rare, and especially that presenting mediastinal tumor was reported to account for only 5% of isolated MS [4], and has been described in only a few case reports [5, 6]. The patient developed multiple extramedullary recurrences without BM infiltration, which is unique even in the context of isolated MS because patients with isolated MS often develop leukemic infiltration of BM during the course [7]. The clinical characteristics of this case, such as primary mediastinal involvement, were not reported to be associated with the distinct clinical course in AML. Thus, *FUS-ERG* gene fusion may be one of the reasons for the uncommon clinical features.

In terms of the transcript subtype, four types of *FUS-ERG* chimeric gene transcript have been reported in AML [1], and this patient had type A and B subtypes. Subtype B is the transcript produced by in-frame fusion, which is frequently found in AML with t(16;21). Subtype A is an out-of-frame transcript, which is thought to be produced by alternative splicing. We confirmed strong expression of ERG protein in the sections both at first presentation and at relapse (data not shown). Therefore, we assume that the fusion protein was expressed in tumor of this patient.

It was reported that chromosomal aberration in BM or peripheral blood blasts was detected in approximately half of patients with MS who developed leukemia, and monosomy 7, trisomy 8 and *MLL* were common abnormalities [8]. Recently, rare fusion genes have been reported in MS, which were related to uncommon clinical manifestations [9]. Although we report for the first time MS with t(16;21) producing *FUS-ERG* chimeric gene transcript, this disease entity might not be so very rare among isolated MS cases because G-banding analysis often cannot detect mitotic cells from solid tumors. In future study, isolated MS with uncommon features should probably be examined by FISH analysis with probes for detecting *FUS-ERG* or other gene fusions.

Optimal therapy for MS has not been determined. AML-type chemotherapy followed by RT for a localized tumor site may be performed for the treatment of patients with isolated MS [10]. In our report, RT was effective for the local control of the disease because the sites of recurrence were outside of the field of RT. Additionally, if a suitable donor is available, allogeneic hematopoietic stem cell transplantation (HSCT) may be effective for isolated mediastinal MS [6]. In fact, given that the patient underwent allogeneic HSCT in non-CR, the disease was well controlled at 2 months after HSCT.

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.

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