Acute myeloid leukemia with t(7;21)(p22;q22) and 5q deletion: a case report and literature review

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Abstract
The gene RUNX1 at chromosome 21q22 encodes the alpha subunit of Core binding factor (CBF), a heterodimeric transcription factor involved in the development of normal hematopoiesis. Translocations of RUNX1 are seen in several types of leukemia with at least 21 identified partner genes. The cryptic t(7;21)(p22;q22) rearrangement involving the USP42 gene appears to be a specific and recurrent cytogenetic abnormality. Eight of the 9 cases identified in the literature with this translocation were associated with acute myeloid leukemia (AML), with the remaining case showing refractory anemia with excess blasts, type 2. Herein, we present a patient with two preceding years of leukopenia and one year of anemia prior to the diagnosis of AML, NOS with monocytic differentiation (myelomonocytic leukemia) whose conventional cytogenetics showed an abnormal clone with 5q deletion. Interphase FISH using LSI RUNX1/RUNXT1 showed three signals for RUNX1. FISH studies on previously G-banded metaphases showed the extra RUNX1 signal on the short arm of chromosome 7. Further characterization using the subtelomeric 7p probe showed a cryptic 7:21 translocation. Our case and eight previously reported leukemic cases with the t(7;21)(p22;q22) appear to share similar features including monocytic differentiation, immunophenotypic aberrancies (often with CD56 and/or CD7), and a generally poor response to standard induction chemotherapy. About 80% of these cases had loss of 5q material as an additional abnormality at initial diagnosis or relapse. These findings suggest that t(7;21) may represent a distinct recurrent cytogenetic abnormality associated with AML. The association between the t(7;21) and 5q aberrancies appears to be non-random, however the pathogenetic connection remains unclear. Additional studies to evaluate for RUNX1 partner genes may be considered for AML patients with RUNX1 rearrangement and 5q abnormalities; however knowledge of the prognostic implications of this rearrangement is still limited.

Keywords: AML, Acute myeloid leukemia, t(7;21), t(7;21)(p22;q22), RUNX1, USP42
the complex karyotype in many AML cases, which makes it more difficult to reveal its significance.

In this study, we describe a new AML case with a cryptic t(7;21)(p22;q22) and chromosome 5q abnormality. The case reported here shares the common features with the few other cases reported in the literature, suggesting that the t(7;21)(p22;q22) may represent a distinct entity in AML.

Clinical presentation
The patient is a 57-year-old female who was referred for hematology consult after presenting with a two-year history of chronic leukopenia with progression to include anemia of several months duration. A bone marrow biopsy was performed, revealing approximately 24% myeloblasts by immunohistochemistry, with the blasts expressing monocytic differentiation with aberrant CD56 expression by flow cytometry. She was diagnosed with AML, and was referred to an academic center for inpatient chemotherapy and possible transplant. Following evaluation, she was placed on Revlimid therapy as opposed to induction chemotherapy for about 5 months without improvement or significant deterioration of her blood counts. She was referred to our institution to be evaluated for allogenic stem-cell transplantation. A repeat bone marrow biopsy (about 6–7 months post diagnosis) confirmed persistent AML, and the patient was started on 7 + 3 AML induction (Cytarabine 320 mg IV continuous days 1–7, Idarubicin 19 mg IV on days 3–6). A day 16 repeat bone marrow biopsy showed persistent presence of abnormal myeloblasts. Biopsy about 6 weeks following induction therapy showed remission with no excess or abnormal myeloblasts. She completed consolidation chemotherapy with high-dose cytarabine (3 gm/m2 IV q 12 hours on days 1, 3, 5 for 6 doses), and recently had a successful allogenic stem-cell transplant.

Materials and methods
Histologic methods
Particle smears and touch preparations were prepared upon receipt of specimen, air dried, and stained with Wright-Giemsa. Trephine biopsy and aspirate clot sections were fixed in B5 and buffered formalin, respectively. Following fixation, tissues were paraffin-embedded, and 4-μm thick sections were cut and stained with hematoxylin-eosin.

Flow cytometry
A WBC suspension is created from the bone marrow aspirate sample using bulk lysing with BD Pharmlyse (ammonium chloride base) and PBS wash. 6-Color custom cocktails (FITC/PE/PerCPy5.5/APC/APCCH7/V450 fluoro chrome format) for immunophenotyping were manufactured by the CTT group of Becton Dickinson. The antibody staining and fixation include a 15 minute incubation in the dark, PBS washing, and resuspension & fixation with 1% paraformaldehyde. The Becton Dickinson FACSCanto II (3-laser) flow cytometer with BD FACSDiva Software were used for event acquisition, and FCS Express Version 3.00.0821 (DeNovo Software, Los Angeles, CA) was used for analysis.

Cytogenetic studies
Conventional chromosome analysis was performed on bone marrow cells using standard cytogenetic techniques and G-banding. A total of 20 metaphase cells were analyzed. Karyotypes were prepared using Applied Imaging CytoVision software and described according to the guidelines of International System for Human Cytogenetic Nomenclature (ISCN, 2013) [7].

Fluorescence in situ hybridization (FISH)
FISH studies were performed on both interphase nuclei and previously G-banded metaphases from the patient’s bone marrow sample. Interphase FISH probes included: EGR1/D5S23-D5S721, D7S486 (7q31)/CEP 7, CEP 8 (D8Z2)/D20S108 (20q12), PML/RARA Dual Color (DC) Dual Fusion (DF), BCR/ABL DC, DF, EVI1 Tri-color (3q26), CBFB DC (16q22), MLL DC (11q23) Break Apart and RUNX1/T1/RUNX1 (ETO/AML1) DC DF probe. Metaphase FISH on previously G-banded slides included RUNX1/T1/RUNX1 (ETO/AML1) DC DF probe, TelVysion 7p, 7q and 14q probe (subtelomeric cocktail). All the probes were from Abbott Molecular (Des Plaines, Illinois 60018).

Figure 1 Aspirate smear, Wright-Giemsa, 100× – cluster of intermediate-sized blasts with irregular nuclear contours, fine chromatin with 1–2 nucleoli, and relatively abundant cytoplasm with occasional small vacuoles and rare azurophilic granules. Rare small lymphocytes and plasma cells are intermixed.
Results
Morphology and immunophenotypic findings
The bone marrow biopsy demonstrated a hypocellular marrow with increased blasts representing about 25% of the cellular marrow elements (Figures 1 and 2). Background hematopoiesis was suppressed and left-shifted, but did not show morphologic evidence of dysplasia. Immunophenotyping of the abnormal blasts by flow cytometry (Figure 3) showed expression of CD10 (partial), CD11b (partial), CD13, CD14 (partial), CD15 (partial), CD16 (partial), intracytoplasmic CD22 (partial), surface CD22 (partial), CD34 (partial), CD36 (partial), CD38, CD56 (partial), CD64 (partial), CD117 (partial), HLA-DR (bright), and Myeloperoxidase (partial). Features of myelomonocytic dysmaturation were present.

Cytogenetic analysis
Chromosome analysis of the bone marrow revealed additional material of unknown origin at 5q13. This unbalanced rearrangement characterized as "add" (ISCN, 2013) led to partial deletion of 5q in 5 of the 20 metaphase cells examined. The initial karyotype was described as: 46,XX,add(5)(q13)[5]/46,XX[15] (Figure 4a). This finding was confirmed by the concurrent interphase FISH study (Figure 4b).

FISH
The RUNX1/RUNXT1 DC DF interphase FISH exhibited three green signals for RUNX1 (Figure 5). FISH studies on previously G-banded metaphases showed that the extra RUNX1 signal was on the short arm of chromosome 7 (Figure 6). Further characterization using the subtelomeric...
probe (TelVysion 7p, 7q and 14q cocktail) confirmed a cryptic 7;21 translocation (Figure 7). Based on the metaphase FISH study, the final karyotype of the bone marrow was characterized as: 46,XX,add(5)(q13)[5]/46,XX[15].ish t (7;21)(p22;q22)(RUNX1+; VIlyRM2185+).

Discussion
In this study, we describe a new case of semi-cryptic t(7;21)(p22;q22) involving the RUNX1 gene and the loss of chromosome 5q in an AML patient. First reported by Paulsson et al. in AML [8], only 9 cases of t(7;21)(p22;q22) have been reported to date (Table 1) [2,8-12]. Literature review shows that t(7;21) is a recurrent cytogenetic abnormality in AML [9-11]. The incidence rate of this abnormality varies among reports but is relatively low; Giguere et al. [2] reported approximately 1% in 95 AML patients, and Jeandidier et al. reported 0.75% in 397 cases of AML.

We compared our case with the other reported t(7;21)(p22;q22) cases (Table 1) [2,8-11]. Of all the 9 reported t(7;21)(p22;q22) cases, eight were diagnosed as AML, and
one as an MDS (RAEB-2). In all reported AML patients with t(7;21)(p22;q22) including our current case, the common features in these patients include: 1) Aberrant CD56 expression (8/9 patients) and aberrant CD7 expression (6/9 patients). No patients had expression of CD19, which is commonly seen in t(8;21) [13,14]. 2) Myelomonocytic or monocytic differentiation was common (6/9), and 3/9 patients did not show maturation or showed minimal differentiation. 3) Patients responded poorly to the standard induction chemotherapy. 4) Eight of the 9 patients had loss of chromosome 5q at the initial diagnosis or at relapse.

CD56 expression is seen in about 25% [15,16] of AML cases with t(8;21) (q22;q22), and is generally associated with poor prognosis [16]. Meanwhile, CD7 is expressed in about 30% of AML cases and its positivity is linked with poor prognosis in myeloid malignancies [17]. The t(7;21)(p22;q22) AML cases had CD56 and CD7 positive rates higher than what has been reported in general AML cases, and these patients had an overall poor response to standard chemotherapy (Table 1).

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As previously noted, deletion of 5q is a common cytogenetic abnormalities in 8 of the 9 patients with t(7;21) (p22;q22). The high incidence of t(7;21)(p22;q22) found together with del(5q) suggest that this combination is a non-random abnormality. Many questions need to be answered, including: Why does this combination happen with such a high frequency? What is the etiology? What is the significance of these aberrations in relation to AML? Although a recent large scale cooperative study of 514 MDS patients showed that 5q deletion with additional cytogenetic abnormalities is a marker of poor prognosis [20], additional study is needed for this combination in AML. While we cannot provide further experimental evidence, we think one possibility is that two (or more) functionally redundant genes were disrupted by the t(7;21)(p22;q22) and del(5q) respectively. Subsequently, the affected cells would have lost important...
### Table 1 Reported cases with t(7;21)(p22;q22)

| Report                  | Case | Diagnosis/Subtype                | Age/Sex | Flow aberrancies | Induction regimen | Remission post-induction | Sq abnormalities | Outcome                                                                 |
|-------------------------|------|----------------------------------|---------|------------------|-------------------|-------------------------|-----------------|--------------------------------------------------------------------------|
| Index case              | 1    | Monocytic                        | 56 yo, F| CD7, CD56        | Cytarabine/Idarubicin “7+3” | Yes                      | Yes             | CR 51 days s/p induction. Completed consolidation and recently underwent unrelated SCT |
| Paulsson, et al. [8]    | 2    | Minimal differentiation          | 7 yo, M | Partial CD56     | NOPHO-AML-93 protocol | No                       | Yes             | (at relapse) Relapse at 5 years with successful re-induction             |
| Foster, et al. [9]      | 3    | Monoblastic/Monocytic            | 68 yo, M| NA               | MdAC              | No                       | No              | Dead at 5 years from unrelated illness                                  |
| Giguère, et al. [2]     | 4    | Without maturation               | 32 yo, M| CD7, CD56        | Cytarabine/Daunorubicin | NA                       | Yes             | Died of fungal infection within months of dx                            |
| Jeandidier, et al. [10] | 5    | Myelomonocytic vs. Monoblastic/Monocytic | 54 yo, M| CD2, CD7, CD22, CD56 | GOELAMS           | No                        | Yes             | Relapse at 23 months, DOD                                              |
|                         | 6    | Monoblastic/Monocytic            | 33 yo, M| CD7, CD56        | SHG AML96         | No                        | Yes             | CR after salvage chemo and allogenic transplant, alive at 36 months     |
|                         | 7    | Myelomonocytic                   | 39 yo, M| CD22, CD56       | Cytarabine/Idarubicin | No                        | Yes             | Partial response to salvage chemo, dead of bacterial sepsis within months of dx |
| Gindina, et al. [12]    | 8    | Myelomonocytic                   | 13 yo, M| CD7, CD56, CD71  | AIE/HAM           | No                        | Yes             | Remission after consolidation chemo, No long-term survival data reported |
| Panagopoulos, et al. [11]| 9   | Without maturation               | 52 yo, F| CD7, CD56        | “Standard induction” | NA                       | Yes             | In remission at nine months post dx, no long-term survival data reported |
| MDS                     | 10   | RAEB-2 (17% blasts)              | 68 yo, F| NA               | Mylotarg, Daunorubicin, Clofarabine | Yes                      | No              | Remained in remission post maintenance chemotherapy                    |

**Abbreviations:** NA not available, MIDAC Mitoxantrone and cytarabine, GOELAMS groupe ouest-est des Leucémies et Autres Maladies du Sang 2001 AML protocol, DOD died of disease, SHG AML96 süddeutsche hämoblastose-gruppe protocol, CR complete remission, AIE cytarabine idarubicin etoposide, HAM high dose cytarabine and mitoxantrone.
functions associated with drug resistance, apoptosis, and/or DNA repair.

All previous reports about the t(7;21)(p22;q22) rearrangement have detected a RUNX1-USP42 fusion protein. It is reasonable to assume that our case also has the associated RUNX1-USP42 fusion protein, although we did not pursue the exact partner of RUNX1 in this report due to the limited specimen. RUNX1 is a vital regulator of hemopoiesis [21]. Various hemopoietic signaling molecules, growth factors, and transcription factors are regulated by RUNX1 [22]. RUNX1 translocation is a recurrent feature in many AML and MDS patients, and numerous translocation partners have been described. RUNX1 rearrangement’s leukemogenicity lies in the retention of RUNX1’s DNA binding “Runt homology domain” (RHD) domain, and associated loss of its transactivation domain. The resultant fusion protein acts as a dominant negative inhibitor of wild-type RUNX1 in transcription activation [11,22].

While most studies focus on RUNX1, ubiquitin specific peptidase 42 (USP42) may also play an important leukemogenic role in t(7;21)(p22;q22) cases. USP42, belonging to the ubiquitin-proteasome system (UPS), is a deubiquitinating enzyme (DUB). The process of ubiquitination and deubiquitination decides the fate of many proteins, many of which are related with cell cycle regulation, DNA repair, and differentiation. UPS and the DUBs contain many potential drug targets for the treatment. USP42 itself was reported to increase the stability of p53 [23]. We propose that RUNX1-USP42 fusion protein loses wild type USP42 function and decreases the stability of p53. Further studies to characterize the involvement of USP42 in our case were not possible due to insufficient sample.

In conclusion, we report a new case of AML with a cryptic t(7;21)(p22;q22) and chromosome 5q abnormality. To the best of our knowledge, this represents one of the few AML patients with this genetic aberrancy. Review of the literature showed that our case shares many common features with other reported cases, which suggests that t(7;21)(p22;q22) may represent a new distinct entity in AML.

Consent
Consent for publication of this case report and any accompanying images was obtained from the patient.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
JJ and EL contributed equally to get clinical information, flow cytometry and morphological data as well as the cytogenetic and molecular cytogenetic data. LY did all the bench work in this case as well the interpretation of the results. CAT drafted and checked all the manuscript and this case presentation. All authors read and approved the final manuscript.

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References
1. Mitelman F, Johansson B, Mertens F: The impact of translocations and gene fusions on cancer causation. Nat Rev Cancer 2007, 7:233–245.
2. Guguen A, Heibert J: Microhomologies and topoisomerase II consensus sequences identified near the breakpoint junctions of the recurrent t(7;21)(p22;q22) translocation in acute myeloid leukemia. Genes Chromosomes Cancer 2011, 50:228–238.
3. Ferrando AA, Look AT: Clinical implications of recurring chromosomal and associated molecular abnormalities in acute lymphoblastic leukemia. Semin Hematol 2000, 37:381–395.
4. Golub TR, Barker GF, Bohlender SK, Hiebert SW, Bray-Ward P, Morgan E, Raimondi SC, Rowley JD, Gilliland DG: Fusion of the TEL gene on 12p13 to the AML1 gene on 21q22 in acute lymphoblastic leukemia. Proc Natl Acad Sci USA 1995, 92:4917–4921.
5. Mikhail FM, Coignet L, Hatem N, Mourad Z, Farahat N, Nucifora G: A novel gene, FGAL2, is fused to RUNX1/AML1 in a t(4;21)(q22;21) in a patient with T-cell acute lymphoblastic leukemia. Genes Chromosomes Cancer 2004, 39:110–118.
6. Gagoundis AA, G€erming U, Aul C: Biological and prognostic significance of chromosome 5q deletions in myeloid malignancies. Clin Cancer Res 2006, 12:5–10.
7. Shaffer L, McGowan-Jordan J, Schmid M (Eds): ISCN (2013): An International System for Human Cytogenetic Nomenclature. Basel, S. Karger; 2013.
8. Paulsson K, Bekassy AN, Olofsson T, Mitelman F, Johansson B, Panagopoulos I: A novel and cytogenetically cryptic t(7;21)(p22;q22) in acute myeloid leukemia results in fusion of RUNX1 with the ubiquitin-specific protease gene USP42. Leukemia 2006, 20:224–229.
9. Foster N, Paulsson K, Sales M, Cunningham J, Groves M, O’Connor N, Begum S, Stubbe T, McMullan DJ, Griffiths M, Pratt N, Tauer S: Molecular characterisation of a recurrent, semi-cryptic RUNX1 translocation t(7;21) in myelodysplastic syndrome and acute myeloid leukaemia. Br J Haematol 2010, 148:938–943.
10. Jeandillier E, Gervais C, Radford-Weiss I, Zink E, Gangneux C, Eischen A, Haddad E, Viguier F, Dreyfus F, Varet B, Flandrin G, Macintyre E, Morgan E, Raimondi SC, Rowley JD, Gilliland DG: Detection of t(8;21)/AML1-ETO in AML M1/M2: correlation with cytogenetics, morphology and immunophenotype. Br J Haematol 2007, 139:148–153.
11. Panagopoulos I, Gorunova L, Brandal P, Garnes M, Tierens A, Heim S, Martzolf L, Drenou B, Lioure B, Tancredi C, Rimelen V, Mauvieux L: A cytogenetic study of 397 consecutive acute myeloid leukemia cases identified three with a t(7;21) associated with 5q abnormalities and exhibiting similar clinical and biological features, suggesting a new, rare acute myeloid leukemia entity. Cancer Genet 2012, 205:365–372.
12. Van Ommen B, Beernink DJ, Vriesendorp H, Veen C, Eggen HJ, Zwinderman AH, Van Tinteren H, Creutzberg EC, Van der Warnken H: The impact of translocations and associated molecular abnormalities in acute lymphoblastic leukemia. Int J Lab Hematol 2008, 30:154–1552.
13. Huret JL, Br J Haematol 2010, October 2007. http://AtlasGeneticsOncology.org/Anomalies/t0721/p22q22/11449.html.
14. Andreiu V, Radford-Weiss I, Troussard X, Chane C, Valensi F, Guesnu M, Haddad E, Viguier F, Dreyfus F, Varet B, Flandrin G, Macintyre E: Molecular detection of t(8;21)/AML1/ETO in AML M1/M2: correlation with cytogenetics, morphology and immunophenotype. Br J Haematol 1996, 92:865–865.
15. Khouy H, Dalal BI, Nevill TJ, Horsman DE, Barnett MJ, Shepherd JD, Toze CL, Conneally EA, Sutherfield HJ, Hogg DE, Nanteau SH: Acute myelogenous leukemia with t(8;21): identification of a specific immunophenotype. Genes Chromosomes Cancer 2003, 34:173–1718.
16. Chen SW, Li CF, Chuang SS, Tseng CC, Hsieh YC, Lee PS, Chen CH, Huang WT, Hwang WS, Tsao CJ: Aberrant co-expression of CD19 and CD56 as surrogate markers of acute myeloid leukemias with t(8;21) in Taiwan. Int J Lab Hematol 2008, 30:133–138.
17. Raspadon D, Danzani D, Lenoci M, Rondelli D, Testoni N, Nard G, Sestigiani C, Mariotti C, Bittolo S, Tozzi M, Laura F: CD56 antigenic expression in
Acute myeloid leukemia identifies patients with poor clinical prognosis. Leukemia 2001, 15:1161–1164.

17. Rohrs S, Scherr M, Romani J, Zaborski M, Drexler HG, Quentmeier H: CD7 in acute myeloid leukemia: correlation with loss of wild-type CEBPA, consequence of epigenetic regulation. J Hematol Oncol 2010, 3:15.

18. Ebert BL, Pretz J, Bosco J, Chang CY, Tamayo P, Galili N, Raza A, Root DE, Attar E, Ellis SR, Golub TR: Identification of RPS14 as a 5q- syndrome gene by RNA interference screen. Nature 2008, 451:335–339.

19. Boultonwood J, Pellagatti A, McKenzie AN, Wainscoat JS: Advances in the 5q- syndrome. Blood 2010, 116:5803–5811.

20. Mallo M, Cervera J, Schanz J, Such E, Garcia-Manero G, Luno E, Steidl C, Espinet B, Vallespi T, Germing U, Blum S, Ohyashiki K, Grau J, Pfeistockler M, Hernandez JM, Noesslingler T, Giagounidis A, Aul C, Gallanz MJ, Martin ML, Valnet P, Collado R, Hafnerfach C, Fonatsch C, Lubbert M, Sauder R, Hildebrandt B, Krieger O, Pedro C, Arenillas L, et al: Impact of adjunct cytogenetic abnormalities for prognostic stratification in patients with myelodysplastic syndrome and deletion 5q. Leukemia 2011, 25:110–120.

21. Okuda T, van Deursen J, Hiebert SW, Grosveld G, Downing JR: AML1, the target of multiple chromosomal translocations in human leukemia, is essential for normal fetal liver hemopoiesis. Cell 1996, 84:321–330.

22. Laufer EM, Winkens MH, Narula J, Hofstra L: Molecular imaging of macrophage cell death for the assessment of plaque vulnerability. Arterioscler Thromb Vasc Biol 2009, 29:1031–1038.

23. Hock AK, Vigneron AM, Carter S, Ludwig RL, Vouilson KH: Regulation of p53 stability and function by the deubiquitinating enzyme USP42. EMBO J 2011, 30:4921–4930.

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