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STAT5b-RARa-positive acute myeloid leukemia: Diagnostic and therapeutic challenges of a rare AML subtype

1. Brief communication

Acute promyelocytic leukemia (APL) is characterized by the specific chromosome translocation t(15;17) involving the *promyelocytic leukemia gene* (PML) on chromosome 15q22 and the *retinoic acid alpha gene* (RARa) on chromosome 17q21. The resulting PML-RARa fusion gene is the hallmark of the disease and is detectable in about 98% of patients using fluorescence in situ hybridization (FISH) or reverse transcription-polymerase chain reaction (RT-PCR). APL characterized by the typical PML-RARa fusion is highly sensitive to all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO) and is curable by using these targeted agents without conventional chemotherapy in the majority of cases [1,2]. In rare instances of morphologically defined APL (1–2% of cases), new fusion proteins have been identified involving RARa and alternative genes other than PML. These include: (i) NPM1-RARa and NuMa-RARa, which are sensitive to therapy with ATRA; (ii) PLZF-RARa, ZBTB16-RARa and STAT5b-RARa fusion genes known to be resistant to ATRA, ATO and frequently also to standard chemotherapy used for acute myeloid leukemia (AML) [3,11].

The AML variant characterized by STAT5b-RARa fusion gene is an extremely rare form with morphologic and immunophenotypic features very similar to classic PML-RARa-positive APL. To date, only eleven cases have been described in the literature, and almost all were diagnosed in young adult males. The prognosis of acute leukemia with the STAT5b-RARa fusion is unfavorable due to resistance to either ATRA or ATO and frequently to conventional chemotherapy [4,5]. We report here a new case of STAT5b-RARa-positive AML focusing on its molecular features and clinical outcome (Fig. 1).

A 47-year-old male came to our observation for isolated neutropenia. His CBC disclosed a WBC count of 1.60×10^9/L, absolute neutrophil count of 0.86×10^9/L, Hb level 13.2 g/dl, and a platelet count of 229×10^9/L. Liver and kidney functional tests as well as coagulation parameters were normal. The patient had neither relevant anamnestic antecedents nor history of drug intake. Clinical examination showed no relevant signs and the patient refused further laboratory tests including bone marrow aspirate. Eight months later, he was admitted for severe fatigue, and a new CBC showed Hb 10 g/dl, WBC 2.00×10^9/L, ANC 0.32×10^9/L, Plt 123×10^9/L, and a slight reduction of fibrinogen levels (122 mg/dl). The bone marrow examination disclosed infiltration (70%) by hypergranular and dysplastic promyelocytes with bilobed nuclei and Auer rods. An immunofluorescence assay for PML nuclear distribution analysis showed a nuclear body pattern ruling out PML/RARa-positive APL. Immunophenotypic characterization showed positivity for CD33(++) MPO(++) CD13(+) and negative staining for CD34 and HLA/DR. Cytogenetic analysis disclosed a 46 XY karyotype, with der(5)t(5;8) in 11 metaphases, while FISH analysis performed with RARa dual-color break-apart rearrangement probe showed del(17)(5′RARa +, 3′RARa-) in 80% of cells. The microdeletion involving the distal region of RARa has been described in the reported cases of AML with STAT5b-RARa fusion [2,3], whose presence was subsequently identified by RT-PCR, using the primers and PCR protocol reported by Grimwade et al. [2]. The amplified transcript was sequenced by Sanger method, which disclosed the fusion of STAT5b exon 14 with RARa exon 3. Expression of the STAT5b-RARα transcript was confirmed using nested RT-PCR as reported [6,8]. No mutations in the FLT3 gene were detected as also reported by others [7].

Based on morphologic and immunophenotypic suspicion of APL, the patient was initially treated with ATRA (45 mg/m^2), however no improvement in either hematologic response or coagulation parameters were observed after one week. Following the results of FISH analysis, ATRA was discontinued and intensive chemotherapy was started with standard doses of Daunorubicin and ARA-C. A bone marrow aspirate following induction chemotherapy showed persistence of leukemic blasts (60%). In view of resistant disease the patient received salvage chemotherapy consisting of the FLAG-IDA regimen in association with ATRA. A bone marrow examination after re-induction showed a complete morphologic remission with a minimal residual disease (MRD) level of 2% as detected by flow cytometry. In view of the complete remission (CR) achievement and the high relapse risk, the patient underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) from an HLA-matched sibling donor.

A bone marrow aspirate carried out at day 16 after allo-HSCT showed severe aplasia without presence of blasts. Analysis for the STAT5b-RARa transcript showed absence of detectable fusion by nested RT-PCR. Engraftment occurred at day 31 and the bone marrow examination showed a complete molecular response with full donor chimerism. After a prolonged phase of neutropenia, the patient died of sepsis and multiple organ failure, probably secondary to invasive pulmonary aspergillosis.

The case here reported further indicates that AML with STAT5b-RARa fusion appears to be a leukemic subset with unfavorable prognosis. As also shown by other published reports [9,10], STAT5b-RARa positive AML is frequently resistant not only to ATRA and ATO, but also to conventional intensive chemotherapy such as 7 + 3 or similar regimens.

Almost all patients previously described in the literature (10 out of 11) had received conventional intensive chemotherapy with ARA-C and anthracyclines. Of these, 7 patients achieved CR, however all developed early relapse except for three cases in which the CR was consolidated by allo-HSCT and the death occurred for transplant-related complications. Three patients showed primary resistance to intensive chemotherapy and died of disease progression [4,9].

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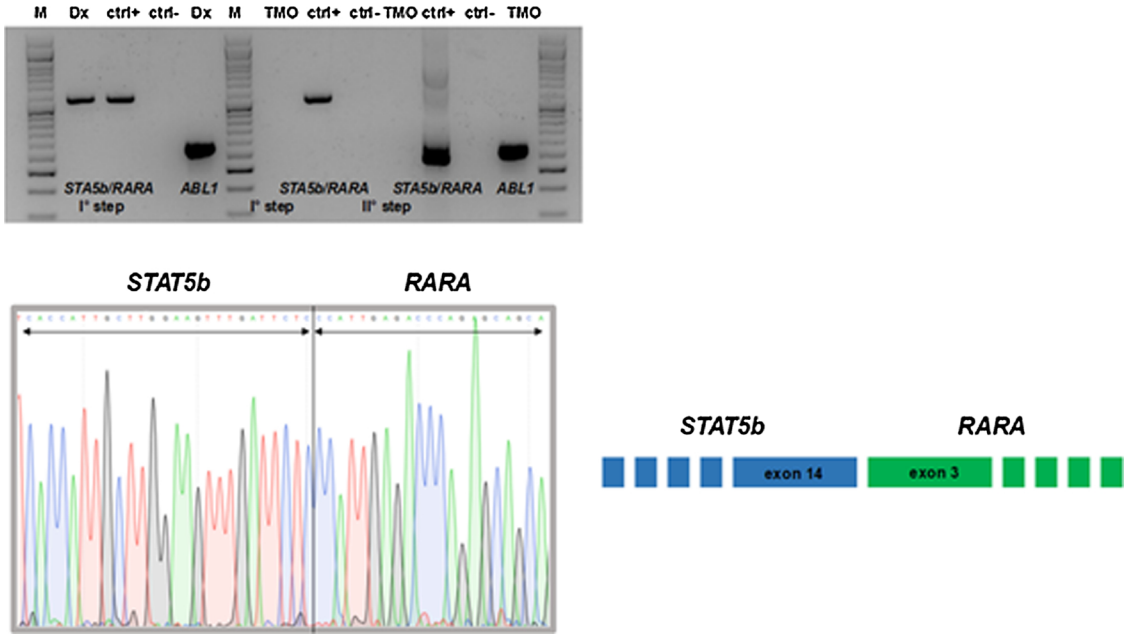

Fig. 1. STAT5b-RARa fusion transcript detected by nested RT-PCR analysis in this patient. RT-PCR sequencing results show the fusion between STAT5b exon 14 and RARa exon 3.

There are very limited data on MRD monitoring in patients with STAT5b-RARa rearrangement and to date only three cases have been reported. Of these, only one patient among the described ones had maintained complete molecular remission at 28 months from alloHSCT and then he died at 52 months for transplant-related complications [7,12]. Therefore, combined to the available evidence from the literature, our findings suggest that patients with STAT5b-RARa-positive AML patients should be allocated after initial therapy to intensive treatment using allogeneic transplant strategies as a remission consolidation.

Despite the rarity of patients with STAT5b-RARa positive AML, molecular MRD monitoring seems important as it might help in better assessing response to therapy.

In conclusion, our case clearly shows the biologic and clinical diversity of STAT5b-RARa cases compared to PML-RARa positive APL, and highlights the importance of STAT5b-RARa identification at diagnosis to correctly address patients to AML treatment strategies.

Authorship contributions

G. Ciangola, L.Cicconi and F. Lo-Coco designed the study, wrote and revised the manuscript

S. Travaglini, T. Ottone, S. Lavorgna, M. Angelini, L. Cicconi: contributed laboratory characterization, analyzed the data and revised the manuscript

C. Gurnari, G. Paterno, M. Mirabile : contributed patients' data and revised the manuscript

Disclosure competing interests statement

The Authors declare no competing financial interest related to this work.

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References

[1] Francesco Lo-Coco, Giuseppe Avvisati, Marco Vignetti, Christian Thiede, Sonia Maria Orlando, Simona Iacobelli, for Gruppo Italiano Malattie Ematologiche dell'Adulto, the German–Austrian Acute Myeloid Leukemia Study Group, Study Alliance Leukemia, et al., Retinoic acid and arsenic trioxide for acute promyelocytic leukemia, N. Engl. J. Med. 369 (2013) 111–121, https://doi.org/10.1056/NEJMoa1300874.

[2] D. Grimwade, A. Biondi, M.-J. Mozziconacci, A. Hagemeijer, R. Berger, M. Neat, et al., Characterization of acute promyelocytic leukemia cases lacking the classic t (15;17): results of the European working party, Blood 96 (August (4)) (2000) 1297–1308.

[3] Julia Adams, Mehdi Nassiri, Acute promyelocytic leukemia: a review and discussion of variant translocations, Arch. Pathol. Lab. Med. 139 (October (10)) (2015) 1308–1313, https://doi.org/10.5858/arpa.2013-0345-RS.

[4] L. Liu, S. Chen, J. Tan, P. Shi, K. Chen, D. Gao, et al., Acute promyelocytic leukemia with Stat5b- RARα fusiongene: a case report and literatures review, Zhonghua Xue Ye Xue Za Zhi 37 (January (1)) (2016) 68–69, https://doi.org/10.3760/cma.j.issn.0253-2727.2016.01.014.

[5] S. Strel, M. Konig, H. Botzug, B.W. Cooper, K. Suzukawa, S.J. Zhang, et al., All-trans retinoic acid and arsenic trioxide resistance of acute promyelocytic leukemia with the variant STAT5B-RARA fusion gene, Leukemia 27 (July (7)) (2013) 1606–1610, https://doi.org/10.1038/leu.2012.371 Epub 2012 Dec 28.

[6] J.V. Jovanovic, K. Rennie, D. Culligan, A. Peniket, A. Lennard, J. Harrison, et al., Development of real-time quantitative polymerase chain reaction assays to track treatment response in retinoid resistant acute promyelocytic leukemia, Front. Oncol. 25 (October (1)) (2011) 35, https://doi.org/10.3389/fonc.2011.00035 Ecollection 2011.

[7] C. Qiao, S.J. Zhang, L.J. Chen, K.R. Miao, J.F. Zhang, Y.J. Wu, et al., Identification of the STAT5B-RARα fusion transcript in an acute promyelocytic leukemia patient without FLT3, NPM1, c-Kit and C/EBPα mutation, Eur. J. Haematol. 86 (May (5)) (2011) 442–446, https://doi.org/10.1111/j.1600-0609.2011.01595.x.

[8] H. Chen, J. Pan, L. Yao, L. Wu, J. Zhu, W. Wang, et al., Acute promyelocytic leukemia with a STAT5b-RARα fusion transcript defined by array-CGH, FISH, and RT-PCR, Cancer Genet 205 (June (6)) (2012) 327–331, https://doi.org/10.1016/j.

cancergen.2012.02.007.
[9] C. Zhang, Y. Wang, B. Liu, B. Gong, X. Gong, Y. Liu, et al., Clinical characteristics of acute promyelocytic leukemia with the STAT5B-RARA fusion gene, Blood Cells Mol. Dis. 69 (March) (2018) 71–73, https://doi.org/10.1016/j.bcmd.2017.09.007.
[10] Y.Y. Wang, J. Hao, Z.Y. Liu, X.Q. Weng, Y. Sheng, C.L. Jiang, et al., Novel STAT5B-RARA fusion transcript in acute promyelocytic leukemia: identification and treatment response, Leuk. Lymphoma 56 (9) (2015) 2731–2734, https://doi.org/10.3109/10428194.2015.1007454 Epub 2015 Feb 11.
[11] Y. Lou, Y. Ma, J. Sun, X. Ye, H. Pan, Y. Wang, et al., Evaluating frequency of PML-RARA mutations and conferring resistance to arsenic trioxide-based therapy in relapsed acute promyelocytic leukemia patients, Ann. Hematol. 94 (November (11)) (2015) 1829–1837.
[12] M.J. Kluk, R.P. Abo, R.D. Brown, Kuo Fc, P. Dal Cin, O. Pozdnyakanova, et al., Myeloid neoplasm demonstrating a STAT5B-RARA rearrangement and genetic alterations associated with all-trans retinoic acid resistance identified by a custom next-generation sequencing assay, Cold Spring Harb. Mol. Case Stud. 1 (October (1)) (2015) a000307, , https://doi.org/10.1101/mcs,a000307.

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