Clinical characteristics and treatment outcome of an 86 year-old patient with Acute Myeloid Leukaemia with Acute Promyelocytic-like Morphology and uncommon RARA fusion variant

Roberto Castelli[1*], Valentina Rossi[2], Matteo Giovanni Della Porta3, Riccardo Schiavon[1], Marco Barchiesi[1], Laura Cicconi[4] and Francesco Lo Coco[4]

Keywords: Promyelocytic leukaemia, promyelocytes, bone marrow, diagnosis

Abstract: Acute promyelocytic leukaemia (APL) is a sub classification of acute myeloid leukaemia (AML) characterised by the translocation t(15;17) (q22;q21) generating the PML-RARA fusion gene. In rare cases of AML with APL like morphology, RARA can be merged to an another partner other than PML (e.g. PLZF, NPM1, NUMA1, STAT5B, PRKAR1A and others) and this genetic heterogeneity accounts for the different sensitivity to targeted agents, such as all-trans retinoic acid (ATRA) and arsenic trioxide (ATO). An 86-year-old man was referred to our hospital because of pancytopenia. Complete blood count (CBC) showed blood cells 4.190/µL (segment neutrophils 17%; lymphocytes 11%; monocytes 11%; eosinophils 1%; basophils 0%; leukemic cells 58%, metamyelocytes 2%); haemoglobin 97 g/L; and platelets 34.000/µL. Bone marrow biopsy revealed about 100% cellularity, and 80% of the nucleated elements were leukemic cells. The leukemic cells showed medium to large size, irregular shape, finely chromatinized nuclei with distinct nucleoli and multiple Auer rods. Flow cytometric analysis demonstrated that the blast population unveiled high side scatter features and expressed bright CD33; dimCD117; dimCD13; dimCD14; and was essentially negative for HLA-DR and CD34. Due to the suspect of acute promyelocytic leukaemia (APL), therapy with ATRA was promptly started without observing improvement in haematological parameters. The patient did not have clinical coagulopathy nor did he develop signs of differentiation syndrome. Cytogenetic G-band analysis identified an aberration involving 17q in 26/28 metaphases obtained. Metaphase fluorescent in situ hybridisation studies revealed a rearrangement involving RARA at 17q12 and karyotype was 45,X0, add(8)(q24), t(11;17) (q23;q12). Standardised reverse transcription-PCR approach confirmed the absence of PML-RARA transcripts (Fig. 1). Taking into account that several variant RARA translocations have been reported in acute promyelocytic leukaemia (APL), we performed an NGS approach utilising a gene panel to detect additional mutations. Rearrangement and molecular testing confirmed ZBTB16-RARA RNA fusion transcripts, which usually displays unresponsiveness to ATRA therapy although it must be noted that some response to ATRA therapy has been documented in very rare cases, always in combination with other agents. Thus, the patient was treated with ATRA 45 mg/m2 and cytarabine 40 mg/m2 for 10 days every month.

Three cycles of such treatment resulted in a reduction of transfusion need, increase in platelet count, reduction to 20% of immature promyelocytes. Cytogenetic analysis revealed the presence of only 2 clones carrying 45, X0, add(8) (q24), t(11;17) (q23;q12) and a normal karyotype in the remaining 32 metaphases. After 6 cycles (6 months after the diagnosis), the patient was transfusion free, had normal blood count, the bone marrow exam resulted in 3% of immature promyelocytes, normal cytogenetic pattern and negativity of ZBTB16-RARA RNA fusion transcript. Twelve months after the diagnosis, the patient is still in haematological, cytogenetic, and molecular remission and maintenance therapy consists of ATRA 15 days/month and ARAc 40 mg/mq sc for 10 days every month.

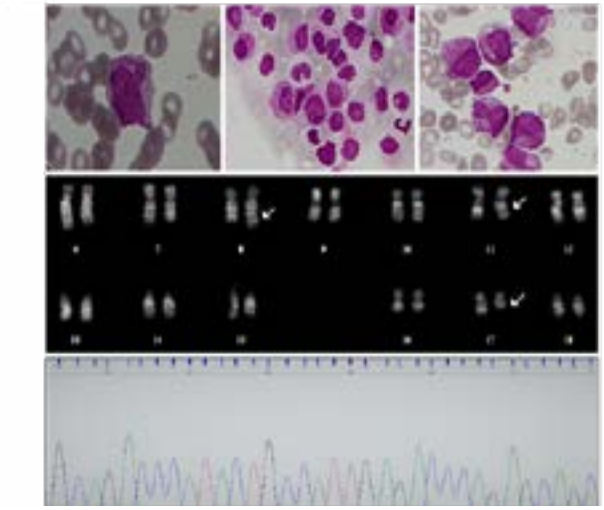

Fig. 1 Panel a Peripheral blood smear showing hypergranular blasts with Auer rods. Panels b, c Bone marrow aspirate showing leukemic cells with medium to large size, irregular shape, finely chromatinized nuclei with distinct nucleoli and moderate amount of blue cytoplasm with azurophilic granules and multiple Auer rods. Panel d Cytogenetic G-band analysis identifying add (8)(q24) and t(11;17) (q23;q12). Panel e Sequencing analysis of ZBTB16-RARA fusion transcript at breakpoint junction

The suspicion of APL generally arises from morphologic examination of the bone marrow, showing the characteristic infiltrate of abnormal hyper granular promyelocytes. A timely morphological diagnosis is of fundamental importance in the diagnosis of APL, since an immediate start of therapy with ATRA and an intensive support with plasma and platelet concentrates, already based on the only morphological suspicion, before molecular confirmation, is able to reduce mortality by cerebral haemorrhage. In the case that we present here, the morphological aspect was so suggestive of APL that it led us to look for other mutations due to the negativity for PML/ RAR alpha. The age of the patient and the potential cardiotoxicity of antracyclines, have made us opt for ATRA and low doses of cytarabine instead of anthracyclines. The search for rearrangements involving RARA gene is essential to confirm diagnosis but also to promptly start tailored therapy and to monitor minimal residual disease. A comprehensive molecular profiling is vital in the presence of suggestive morphological features of PML and in the absence of pathognomonic genetic lesion. It is unclear whether these atypical mutations may retain a prognostic role but some centres treat these patients with ATRA and ATO to completely eradicate the disease. The challenge in this case was to continue with ATRA despite the possible resistance.

Roberto Castelli[1], Valentina Rossi[2], Matteo Giovanni Della Porta[3], Riccardo Schiavon[1], Marco Barchiesi[1], Laura Cicconi[4] and Francesco Lo Coco[4]*

[1]*Department of Biomedical and Clinical Sciences Luigi Sacco, Luigi Sacco Hospital Milan, University of Milan, Milan, Italy*
[2]*Hematology & Transfusion Medicine L. Sacco University Hospital & School of Medicine, Milan, Italy*
[3]*Cancer Center, Humanitas Research Hospital, Humanitas University, Rozzano, Milan, Italy*
[4]*Department of Biomedicine and Prevention, University of Tor Vergata, Rome, Italy*