Acute promyelocytic leukaemia (APML) with cryptic PML-RARA fusion has a clinical course comparable to classical APML with t(15;17)(q24.1;q21.2) translocation

Acute Promyelocytic Leukaemia (APML) with Cryptic *PML-RARA* Fusion Has a Clinical Course Comparable to Classical APML with t(15;17)(q24.1;q21.2) Translocation

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Keywords
Acute promyelocytic leukaemia
Acute myeloid leukaemia
Cryptic translocation
*PML-RARA*
Acute promyelocytic leukaemia (APML) is a rare variant of acute myeloid leukaemia characterised by a distinct clinical presentation, morphology, molecular pathogenesis and prognosis. Patients often present as a medical emergency, with disseminated intravascular coagulopathy (DIC) occurring frequently and resulting in associated haemorrhagic and thrombotic complications. Early therapeutic intervention with all trans retinoic acid (ATRA) demonstrated a significant reduction in early haemorrhagic death. Management of thrombocytopenia, hypofibrinogenaemia and coagulopathy is also crucial in the early stages to minimize this risk. Therefore, prompt initiation of therapy is indicated when APML is suspected until the diagnosis is confirmed or refuted. (Breen et al., 2012)

An underlying reciprocal translocation occurring between chromosome 15 and 17, t(15;17)(q24.1;q21.2), results in the formation of a PML:RARA fusion protein which underlies the molecular pathogenesis of the disease in over 90% of cases. (Grimwade et al., 2000) This abnormality is detectable by cytogenetics, fluorescence in situ hybridization (FISH), real time polymerase chain reaction (RT-PCR) or next generation sequencing techniques. APML occurring with alternative translocations involving the RARA gene including PLZF:RARA resulting from t(11;17)(q23;q21.1) occurs in approximately 1% of patients. Rare reports document the presence of PML:RARA fusion occurring in the absence of the t(15;17)(q24.1;q21.2) translocation and undetectable by FISH. (Rashidi and Fisher, 2015) These cases which are detectable only by RT-PCR are described as cryptic rearrangements. We present the largest individual reported series with long term follow-up of five patients with cryptic APML treated in our institution since 2004. Using a series of eight consecutive classical APML cases as comparators we demonstrate a clinical course that is comparable to classical APML when managed with the same approach.

Table 1 shows the demographics and presenting features of the five cryptic cases and eight classical comparators. Cryptic cases were significantly younger than the classical cases when unpaired two tailed students t-test was used. We also noticed a trend towards a higher rate of leukocytosis, laboratory tests indicative of DIC and rates of thrombosis and haemorrhage. Given the sample numbers of patients involved, we would not comment on the significance of these findings. We also observed that cryptic PML:RARA fusions could produce a disease phenotype that included both hyper-granular and micro-granular morphological variants and leukopenia or leukocytosis. We also observed the presence of breakpoints occurring in all three of the common PML gene breakpoint cluster regions (BCR1, BCR2 and BCR3) breakpoints in cryptic cases. Karyotype was completely normal in four of the cases with trisomy 8 the only abnormality reported in the remaining case.

<table>
<thead>
<tr>
<th></th>
<th>Cryptic</th>
<th>Classical</th>
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</thead>
<tbody>
<tr>
<td><strong>Total Number</strong></td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>43*</td>
<td>65.25*</td>
</tr>
<tr>
<td>Median</td>
<td>33</td>
<td>67.5</td>
</tr>
<tr>
<td>Range</td>
<td>27-77</td>
<td>42-77</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>40%</td>
<td>75%</td>
</tr>
</tbody>
</table>
All five cryptic cases received induction therapy combining anthracycline and ATRA. In one case, the anthracycline was dose reduced. Two patients died in induction therapy, one resulting from pulmonary embolus and one from intracerebral haemorrhage. Of these two deaths, one patient was classed as high risk, while one was classed as low risk using standard APML risk stratification. (Sanz et al., 2000) This compared to one death in induction from infective cause in the classical cases. Anthracycline chemotherapy was withdrawn following two doses in the patient with initial dose reduction due to cardiac complications. Despite this, complete morphological and molecular remission was achieved in all three
cryptic cases surviving induction therapy. Long term remission was achieved following maintenance treatment in two patients to 194 and 139 months respectively. The third patient who received a de-escalated induction therapy had a molecular relapse at 9 months. Following treatment with ATRA and arsenic trioxide, a second complete molecular remission was achieved and been maintained out to 37 months total follow-up. This was comparable to our classical cases were one of the seven patients surviving induction had a clinical relapse at 7 months resulting in death. A further one death occurred from a second malignancy. No other cases of disease relapse occurred.

These five cases of APML resulting from a cryptic PML:RARA rearrangement have demonstrated disease behavior in response to normal APML management that would be expected of disease resulting from the classical t(15;17)(q24.1;q21.2) translocation. We observed a death due to thrombosis and a death due to haemorrhage in induction, a classic feature of APML. In comparison to eight classical cases we noticed a significantly younger age but other features at presentation were generally comparable. There was no significant difference between mortality or relapse between the two groups, although both series are small. Blast count was well above 80% in four of the five cryptic cases making the chances that a false negative result would be obtained from cytogenetic and FISH analysis low and therefore we consider these cases to be genuine cryptic cases. From laboratory records in our institution, since 2004 we have diagnosed 52 cases of acute promyelocytic leukaemia with a PML:RARA rearrangement. This would suggest that the prevalence of cryptic PML:RARA occurring in APML patients in our population is around 9.6%. This is higher than previously estimated,(Grimwade et al., 2000) and may represent an increased tendency in our population or a statistical anomaly due to the low numbers of cases.

From the case series we have presented, we would not recommend any change to patient counselling or management based on the presence of a cryptic PML:RARA fusion. This series highlights the need for vigilance and the use of RT-PCR for PML:RARA detection in FISH negative cases without the t(15;17)(q24.1;q21.2) translocation if a clinical suspicion of APML persists on the basis of clinical and morphological data.

References:

