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t(9;11)(p22;p15) [NUP98/PSIPL] is a poor prognostic marker associated with de novo acute myeloid leukaemia expressing both mature and immature surface antigens

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The \textit{NUP98} gene at 11p15, encoding a nucleoporin that mediates nucleo-cytoplasmic transport of protein and mRNA, is fused with a wide range of different genes via translocations or inversions in haematological malignancies. The vast majority of cases with \textit{NUP98} involvement are acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML) in blast crisis, myelodysplastic syndromes (MDS) and myelodysplastic/myeloproliferative neoplasms, with approximately one quarter being therapy-related [1,2]; only a handful of acute lymphoblastic leukaemia – all of T-cell lineage – has been reported [3]. To date, 25 different partners to \textit{NUP98} have been identified, making \textit{NUP98} one of the most promiscuous genes in neoplasia [3]. However, because of their respective rarity, little is known about the prognostic impact of the various \textit{NUP98} fusion genes/translocations. In fact, reliable outcome data are only available for the t(7;11)(p15;p15) \([\textit{NUP98}/\textit{HOXA}]\), the most common \textit{NUP98} rearrangement [4]. Considering that most AML protocols to a large extent are based on genetic features, it is important to gain insight into the clinical features of also the rare \textit{NUP98} aberrations.

The t(9;11)(p22;p15), leading to a fusion between \textit{NUP98} and \textit{PSIP1} (previously \textit{LEDGF}) [5], has been reported in four AML cases and in one CML in myeloid blast crisis [5-9]. We here report an additional t(9;11)-positive AML and summarise the available clinical data on this cytogenetic subgroup.

A 64-year-old woman without any previous history of malignant disorder, chemo- or radiotherapy was admitted to hospital in November 2006 due to anaemia diagnosed after a period of pneumonia, weight loss and fatigue. At the time of admittance, the white blood cell (WBC) count was 2.5 x 10^9/l, haemoglobin (Hb) 77 g/l and platelets 41 x 10^9/l. Immunophenotypic analysis of the bone marrow (BM) cells revealed that 45% were HLA-DR+, CD117+, CD123+, CD33+, CD13+, CD15+, CD11b+ and CD65+; half were also CD34+, CD2+ and CD135(+). The BM aspirate revealed 50% myeloblasts positive for myeloperoxidase and Sudan B and with morphologic features consistent with acute myeloblastic leukaemia with maturation (AML M2). The cytogenetic analysis yielded the karyotype 46,XX,t(9;11)(p22;p15)[24]/46,XX[1] (Fig. 1A) and fluorescence \textit{in situ} hybridisation analysis showed a fusion of the \textit{NUP98} and \textit{PSIP1} genes (Fig. 1B). Molecular genetic analysis revealed an internal tandem duplication (ITD) of the \textit{FLT3} gene. Morphologic and cytogenetic remission was achieved in March 2007 after two courses of chemotherapy (daunorubicin 60 mg/m^2 d 1-3 and cytarabine 1000 mg/m^2 d 1-5). However, relapse occurred in September 2007, with the same cytogenetic and molecular genetic aberrations as seen at the time of diagnosis. She was treated with cytarabine (1500 mg/m^2 d 1-
but three months later, the BM karyotype showed signs of clonal evolution: 46,XX,t(9;11)(p22;p15)[17]/46,idem,t(1;9;5)(q21;q22;q13)[2]/46,XX[6]. The disease progressed and the patient died in November 2008, two years after the diagnosis.

Including the present case, five t(9;11)-positive AML have now been reported in the literature. As seen in Table 1, the t(9;11) as been the sole cytogenetic abnormality at diagnosis in all cases, in line with other NUP98 rearrangements [2,3]. However, this does of course not exclude the presence of other genetic changes, as exemplified by FLT3 ITD in the present case. Although none of the previously reported AML with t(9;11) had been analyzed for FLT3 aberrations, it may be worthy of note that such changes, as well as various RAS mutations, are frequent in t(7;11)-positive AML [4]. Thus, also AML with NUP98 rearrangements seem to arise through a pathway involving both class I and class II mutations, as suggested as a general mechanism underlying human leukaemias [10].

Approximately 25% of all myeloid malignancies with translocations involving NUP98 are therapy-related, with the frequency varying depending on the type of fusion partner. In general, AML with NUP98 fusions involving homeobox genes are de novo whereas those harbouring NUP98/DDX10, NUP98/TOP1, or NUP98/TOP2B often are associated with previous chemotherapy [2]. All the five t(9;11)-positive AML (Table 1) reported to date have been de novo, suggesting that this subtype belongs to the former group.

It has previously been reported that some NUP98 chimaeras, for example NUP98/HOXA and NUP98/TOP1, are more common in females [2,4]. As regards t(9;11), it may be noteworthy that among the five patients, only one was male. Another similarity between t(7;11)- and t(9;11)-positive AML is also that many of them have an M2 morphology [4, Table 1]. As regards the immunophenotypic features, some markers are recurrent among the three cases where data are available (Table 1), namely CD11b, CD13, CD33, CD34, and HLA-DR. Hence, t(9;11)-positive AML cases seem to be characterized by expression of both mature and immature surface proteins.

Three of the patients (Table 1) are known to have died [9,11, present case]. Furthermore, the patient reported by Ha et al [6] failed to achieve remission after two courses of chemotherapy and the one described by Ahuja et al [5] relapsed after autologous bone marrow transplantation. Thus, the available data strongly suggest that t(9;11) is associated with a poor prognosis, something that we believe should be taken into consideration in clinical decision making.
Conflict of Interest

The authors declare no conflicts of interests.

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Contributions: CL: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted. AH: acquisition of data, final approval of the version to be submitted. KK: acquisition of data, final approval of the version to be submitted. TO: acquisition of data, final approval of the version to be submitted. KP: acquisition of data, drafting the article, final approval of the version to be submitted. BJ: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.
References


Figure legends

Fig. 1. (A) Partial karyotype of the t(9;11)(p22;p15). The arrows indicate the breakpoints. (B) Fluorescence in situ hybridisation analysis revealed a fusion (arrows) between the NUP98 and PSIP1 genes. The bacterial artificial chromosomes RP11-348A20/RP11-120E20 (NUP98; labelled green) and RP11-211N10 (PSIP1; labelled red) were obtained from the BACPAC Resources Center at the Children's Hospital Oakland Research Institute in Oakland, CA (http://bacpac.chori.org).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex/age</th>
<th>Morphology</th>
<th>Immunophenotype</th>
<th>Hb (g/l)</th>
<th>Plts (x 10^9/l)</th>
<th>WBC (x 10^9/l)</th>
<th>Karyotype</th>
<th>Survival (months)</th>
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<tr>
<td>Ha et al (6)</td>
<td>F/20</td>
<td>M1</td>
<td>CD19+, CD22+, CD33+, CD34+, HLA-DR+</td>
<td>104</td>
<td>104</td>
<td>63.8</td>
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<tr>
<td>Ahuja et al (5)</td>
<td>M/52</td>
<td>M1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>+9</td>
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<tr>
<td>Hussey et al (7)</td>
<td>F/60</td>
<td>M2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1.5</td>
<td>46,XX,t(9;11)(p22;p15) 54</td>
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<tr>
<td>Morerio et al (9)</td>
<td>F/5</td>
<td>M2-M3</td>
<td>CD11a+, CD11b+, CD13+, CD34+, CD38+, CD64+,</td>
<td>75</td>
<td>35</td>
<td>207</td>
<td>46,XX,t(9;11)(p22;p15) NR*</td>
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<td>Present case</td>
<td>F/64</td>
<td>M2</td>
<td>CD2+, CD11b+, CD13+, CD15+, CD33+, CD34+,</td>
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<td>41</td>
<td>2.5</td>
<td>46,XX,t(9;11)(p22;p15) 24</td>
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<td>HLA-DR+</td>
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</table>

AML, acute myeloid leukaemia; Hb, haemoglobin; Plts, platelets; WBC, white blood cell count; F, female; M, male; NR, not reported.

*The patient reported by Morerio et al [9] died due to therapy-associated toxicity.