

### First description of the t(10;11)(q22;q23)/*MLL-TET1* translocation in a T-cell lymphoblastic lymphoma, with subsequent lineage switch to acute myelomonocytic myeloid leukemia

In the April 2013 issue of *Haematologica*, Lee *et al.* have described the *TET1* genomic breakpoints and clinical features of *MLL-TET1* rearranged cases of acute leukemia.<sup>1</sup> So far, 13 cases have been reported in the literature, 11 in acute myeloid leukemia (AML) patients<sup>1-8</sup> and 2 in B-cell precursor acute lymphoblastic leukemia (ALL).<sup>9</sup> It was also recently reported that *MLL* is fused to *TET1* in only 5 out of 1,590 *MLL* rearranged AML cases (0.3%).<sup>10</sup> Although those cases are very uncommon, their study can improve our current understanding of leukemogenesis. We report here the first t(10;11) *MLL-TET1* positive case of T-cell lymphoblastic lymphoma occurring in a 31-year old male patient, with a subsequent transformation to AML.

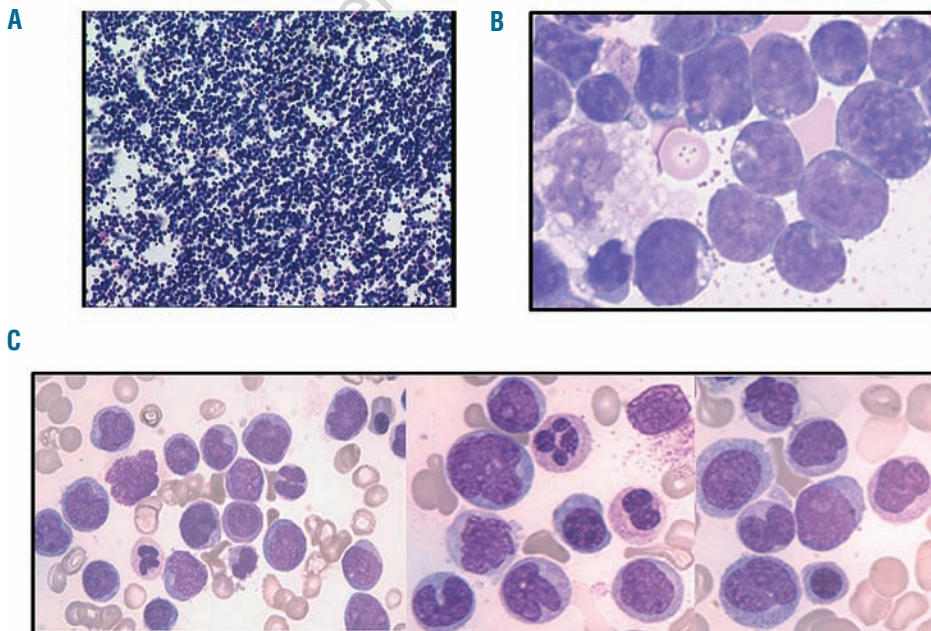
The patient was referred for a large mediastinal mass and right pleural effusion. Blood cell count showed no abnormalities. Mediastinal and bronchus biopsies led to the diagnosis of a precursor-T-cell lymphoblastic lymphoma (pre-T LBL), expressing CD3, CD5, CD4, CD8 and CD10 antigens, together with a high expression of Ki67 (90%). No expression of CD34 or CD79a was observed. The same cells were observed in pleural fluid (Figure 1A and B) that expressed CD3, CD4, CD8, CD2, CD7, CD10 antigens but neither CD34 nor myeloperoxidase. Bone marrow examination and central nervous system imaging did not show any other specific localization. The patient was treated following the Groupe d'Études des Lymphomes de l'Adulte (GELA) LL03 protocol, and was considered in complete remission after induction and consolidation phases. A 32x22x48 mm residual mediastinal mass remained after treatment, without hypermetabolic abnormality on the FDG-PET scan and was considered to be fibronectin scar tissue. Fourteen months after the diagnosis, during the maintenance therapy, a bone marrow examination was performed for thrombopenia (6 g/L) that revealed a myelomonocytic acute leukemia with trilineage

dysplasia (Figure 1C). The mediastinal mass remained unchanged on the imaging scan. The patient achieved complete remission after intensive chemotherapy based on cytarabine and daunorubicin, followed by a consolidation course with high-dose cytarabine. A non-familial donor allogeneic bone marrow transplant (10/10 match) was performed four months after the diagnosis of the acute myeloid leukemia that was complicated by a Grade IV acute graft-versus-host disease involving digestive tract, liver and skin. The patient died 54 days after the transplant of bacterial sepsis leading to multi-organ failure.

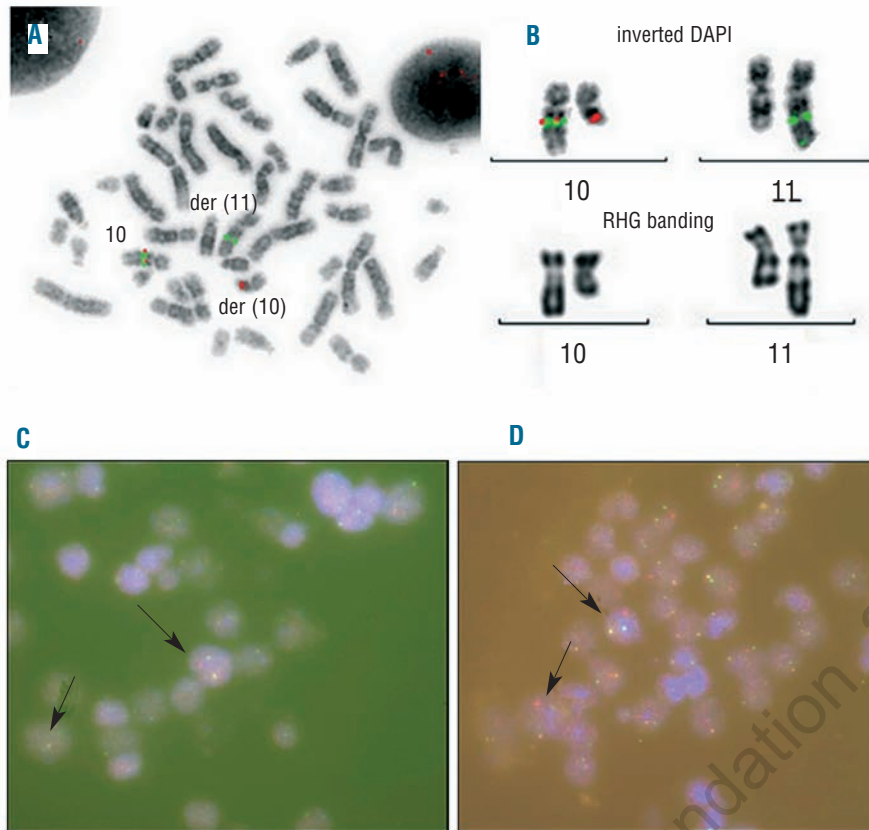
Molecular analyses of the malignant T cells showed a clonal T-cell receptor gamma-chain gene and a minor IgG kappa gene rearrangement (Biomed 2 protocol) together with *HOXA10* overexpression. The presence of *MLL* rearrangement was detected using fluorescence *in situ* hybridization (FISH) analysis (XL *MLL* Break Apart Probe, Metasystems, Altlußheim, Germany). The partner gene, *TET1*, was identified using a RP11-9E13 and RP11-314J18 BACs (BlueGnome, Cambridge, UK (Figure 2), corresponding to the recurrent t(10;11)(q22;q23) translocation. This translocation was found as the sole chromosomal abnormality in blast cells (Figure 2), as frequently observed (4 of 10 cases with available karyotype reported by Lee *et al.*).<sup>1</sup> *MLL-TET1* and its reciprocal fusion transcript were amplified using published primers,<sup>6</sup> and direct sequencing of PCR products showed a fusion of the exon 11 of *MLL* (Ensembl ENSG00000118058) to exon 9 of *TET1* (Ensembl ENSG00000138336), within the main breakpoint cluster of *TET1* localized from exon 8 to 12.<sup>1</sup> In the case reported here, 87 nucleotides of the intron 8 of *TET1* were inserted in the fusion transcript, which contained cryptic splice donor and acceptor sites.

The *MLL-TET1* fusion transcript, as well as *HOXA10* overexpression, was still present at the myelomonocytic acute leukemia phase, but neither *TCR* nor *IGH* rearrangements were detected in the myeloid blasts. Also, neither *NPM* mutation nor *FLT3* internal tandem duplication were observed.

*MLL-TET1* fusions have been described in 11 AML cases (mostly AML M4 or M5) and in 2 B-ALL cases.<sup>1</sup> The case reported here presents two interesting features. Firstly, this



**Figure 1.** Morphology of the malignant cells observed at the two phases of the evolution (A and B) T-cell lymphoblastic lymphoma; (C) myelomonocytic acute leukemia. (A) Section of the embedded pleural cell pellet used for pathology showing a dense infiltration of malignant cells. (B) Cytology of the leukemic cells observed in the pleural fluid. (C) Bone marrow infiltration by monocytic cells, hypogranular myeloid precursors and myeloid blast cells (May-Grünwald-Giemsa staining).



**Figure 1.** Molecular and conventional cytogenetics of bone marrow in the acute myelomonocytic leukemia stage (A and B) and paraffin embedded pleural fluid pellet in the T-cell lymphoblastic lymphoma (C and D). (A) Fluorescent *in situ* hybridization (FISH) analysis using BACs RP11-9E13 (spectrum orange) and RP11-314J18 (spectrum green, BlueGnome®) flanking *TET1* gene that are separated in the t(10;11)(q22;q23) translocation. (B) Magnification of the chromosomes 10 and 11 in inverted DAPI and XL *MLL* break apart probe (Metasystems®) FISH and RHG banding, demonstrating the rearrangement of *MLL*. (C) FISH study using an XL *MLL* break apart probe in pleural effusion. A split of the *MLL* probe had been observed within the malignant cell population (arrows). (D) Interphasic FISH study of *TET1* using BACs probes RP11-9E13 (spectrum orange) and RP11-314J18 (spectrum green). A separation of the signals for one allele had been observed within the malignant cell population.

patient harbors the first *MLL-TET1* fusion reported to date in T-ALL, and, secondly, a lymphoid to myeloid phenotype switch occurred during the course of the disease. Indeed, *MLL-TET1* fusion was detected at both steps, demonstrating a common origin of the two malignancies. This strongly suggests that the translocation occurred very early during hematopoietic differentiation, prior to the lymphoid/myeloid commitment. As described for the Ph1 chromosome rearrangement, the t(10;11) translocation may arise in hematopoietic stem cell rather than in committed progenitors.

Recent studies on *TET1* properties provide a possible explanation as to how such a switch may have occurred. *TET* family enzymes convert 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and play a key role in active DNA demethylation. *TET1* and *TET2* are also the key enzymes responsible for the presence of 5hmC in mouse embryonic stem cells (ESCs), and *TET1* functions to regulate the lineage differentiation potential of ESCs.<sup>11</sup> In addition to its role in DNA demethylation, *TET1* interacts physically with *NANOG*, synergistically enhancing the efficiency of *NANOG* in somatic cell reprogramming in a manner that is dependent on its catalytic activity.<sup>12</sup> *NANOG/TET1* co-occupy genomic loci of genes associated with both maintenance of pluripotency and lineage commitment in embryonic stem cells, and may deposit 5hmC to target genes before the establishment of pluripotency.<sup>12</sup> Taken together, these observations suggest a possible mechanism for the lineage switch observed in this patient, and provide a rationale for using demethylating agents in *MLL-TET1* neoplasms.

On the other hand, *MLL* is a histone lysine specific

methyltransferase frequently rearranged in lineage switching in acute leukemia,<sup>15</sup> and may lead to a stem cell/progenitor phenotype.<sup>14</sup> As both direct and reciprocal transcripts were detected, the respective roles of *TET1* and *MLL* may be additive for lineage switching in this patient.

This case, together with those previously published, indicates that *MLL-TET1* may induce myeloid leukemia, B and T lymphoma, possibly arising from the hematopoietic stem cell compartment. These features are also described in the 8p11 stem cell syndrome that involves *FGFR1*, which arise in myeloid or lymphoid neoplasms with possible subsequent transformation to acute myeloid leukemia. As proposed by Lee *et al.*, we confirm the need to collect and report more cases and to test the leukemogenic activity of *MLL-TET1* associated to demethylating agents in a murine bone marrow transduction/transplantation model system.

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