Acute pro-B-cell lymphoblastic leukemia evolving from myelodysplastic neoplasm post cytotoxic therapy: a case report

Advancements in chemotherapy and the medical care of patients undergoing chemotherapy and radiation treatments have resulted in a growing number of individuals surviving cancer. However, a small percentage of these patients develop secondary hematologic malignancies after anti-cancer treatment. Most are of myeloid origin, including myelodysplastic neoplasm (MDS) and acute myeloid leukemia (AML) post cytotoxic therapy (pCT) which are defined as a distinct category in the current 5th edition of World Health Organization (WHO) classification underscoring their unique nature and the importance of monitoring for these potential complications post-treatment.[1] MDS-pCT and AML-pCT account for approximately 10% to 20% of all MDS and AML cases.[2] Nevertheless, acute lymphoblastic leukemia (ALL) may also develop after cytotoxic therapy for prior malignancy and is referred to as therapy-related ALL (t-ALL).[3,4] The International Consensus Classification 2022 (ICC)[5] adheres to the terminology of therapy-related myeloid neoplasms (t-MDS and t-AML) and includes not only prior exposure to chemotherapy and radiation as causing factors but also immune interventions, e.g., lenalidomide which is routinely used in myeloma therapy. MDS is recognized as a preleukemic event, evolving to AML in approximately 30% of cases.[6] In contrast, the transformation from MDS to ALL is an extremely rare event.[7,8]

In 2002 a 58-year-old woman was diagnosed with breast cancer (ductal carcinoma *in situ*) and was subsequently treated by local surgery and radiation (Figure 1). In June 2011 our laboratory received a bone marrow (BM) sample for the first time from the now 67-year-old patient with suspected multiple myeloma (MM). The patient has given informed consent for genetic analyses as well as the use of laboratory results and clinical data for research purposes according to the Declaration of Helsinki. The study was further approved by the laboratory's institutional review board. BM aspirate showed infiltration of 80% atypical plasma cells (PC) expressing CD38, CD56 as well as CD138 but lacking the expression of CD45 and CD19. Fluorescence *in situ* hybridization (FISH) on BM smears confirmed an aberrant PC clone of about 80% with a trisomy 4, a tetrasomy 11 and a trisomy 15 as well as a subclonal gain of *TP53*/17p (25%). The patient was treated as part of the DSMM XIII phase III trial that investigated the combination of lenalidomide and dexamethasone with or without intensification by high-dose melphalan with autologous transplantation.[9] In brief, induction with lenalidomide and dexamethasone was followed by stem cell mobilization and continued lenalidomide/dexamethasone until progression. Since the time of the subsequent control the MM has been in cytomorphological remission.

After treatment for MM including a total of 21 cycles lenalidomide/dexamethasone a suspected MDS-pCT could not be confirmed by diagnostic work-up of a BM sample (cytomorphology, immunophenotyping, chromosome banding analysis and FISH) in April 2013. However, a retrospective molecular analysis of BM revealed a somatic duplication of the single base guanine within the DNA methyltransferase

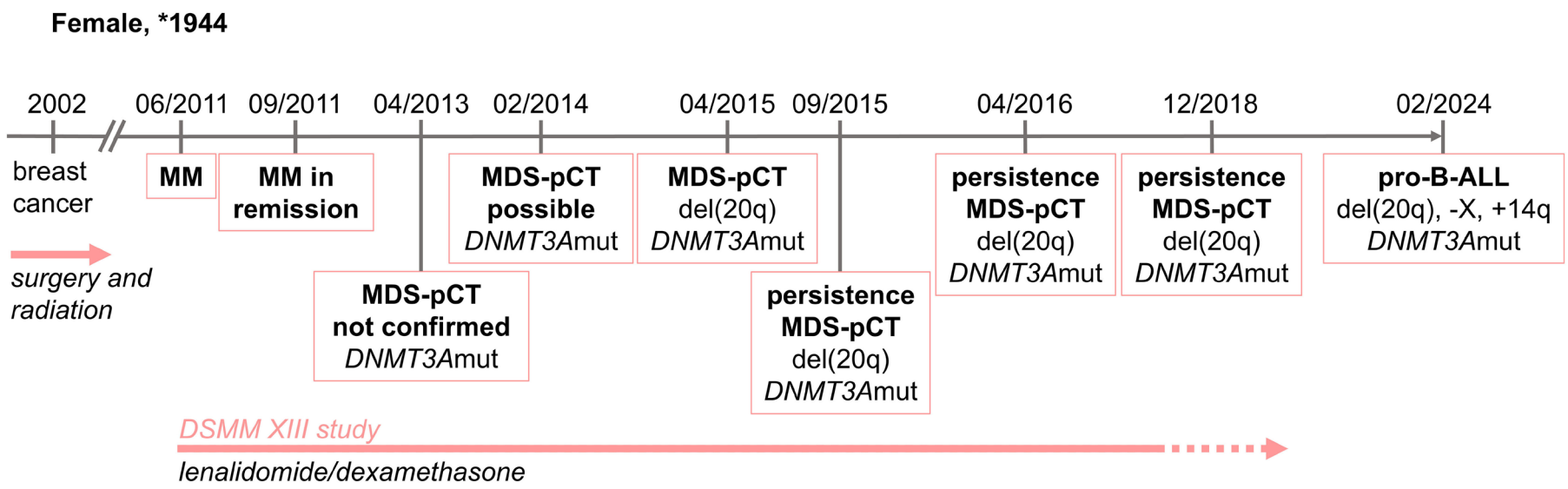

Figure 1. Diagnoses and therapies. Time line of diagnoses and therapies as well as the detection of *DNMT3A* mutation (*DNMT3A*-mut), deletion of chomosome 20q (del(20q), loss of 1 X chromosome (-X) and gain of chromosome 14q (+14q) in the period from 2002 until 2024. MM: multiple myeloma; MDS-pCT: myelodysplastic neoplasm post cytotoxic therapy; pro-B-ALL: acute pro-B-cell lymphoblastic leukemia.

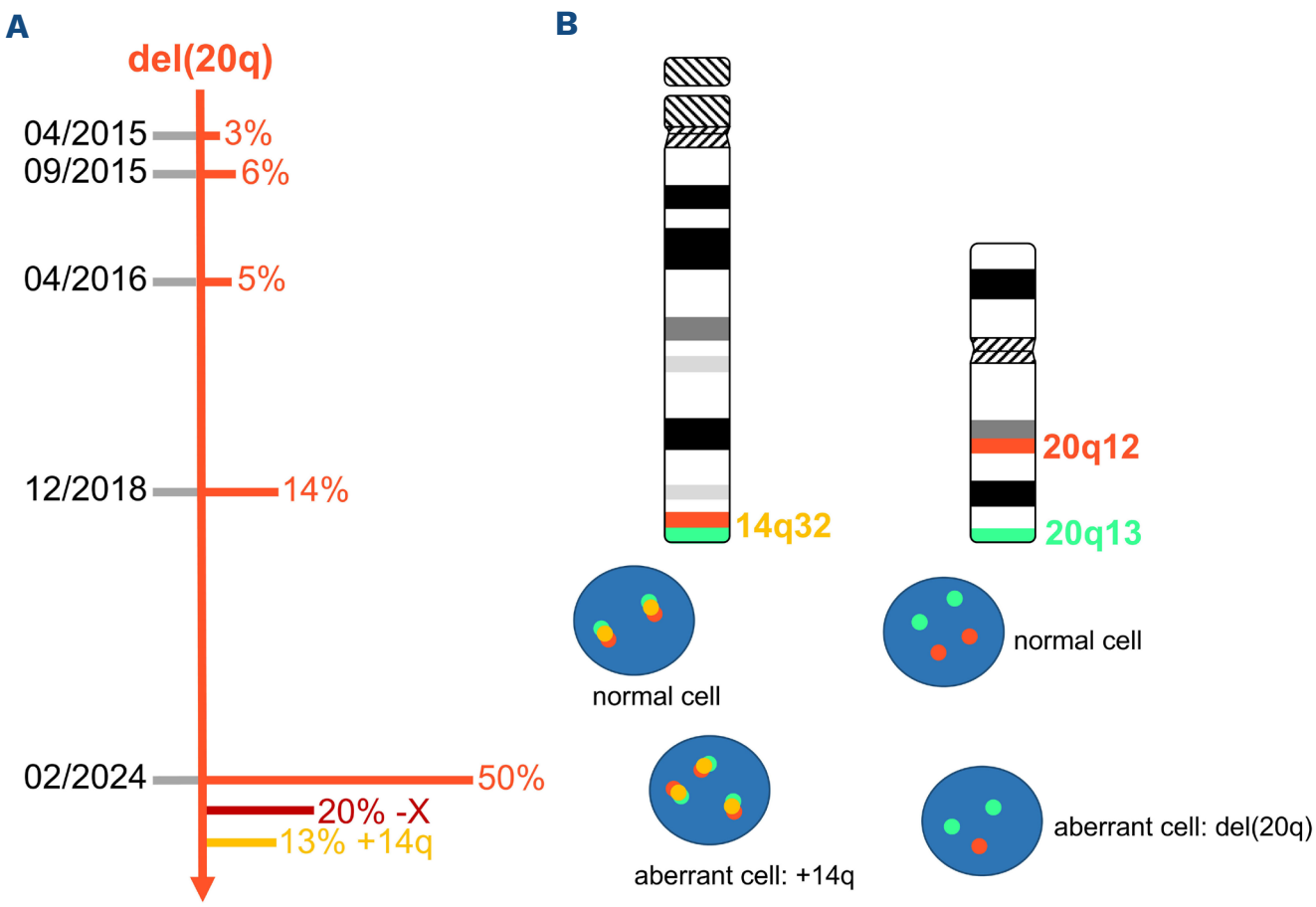

Figure 2. Cytogenetic alterations and fluorescence *in situ* hybridization probes for their detection. Time line of acquired cytogenetic alterations with their respective clone sizes in % from 2015 until 2024 (A). Schematic overview on fluorescence *in situ* hybridization (FISH) probes used for detection of locus 14q32 and loci 20q12 as well as 20q13. Probes for locus 14q32 were break-apart probes which generate co-localized yellow fusion products in a normal non-rearranged locus. In the event of a translocation the colors will split into red and green signals. In case of a 14q gain (+14q) 3 yellow signals are observed. Probes for locus 20q were deletion probes. Cells with deletions at 20q (del(20q)) are identified by a loss of the respective red or green signal (B). -X: loss of 1 X chromosome.

3 α (*DNMT3A*) gene (c.2341dupG) leading to a truncated DNMT3A protein (p.Asp781Glyfs*17) that was initially detected in 2015 for the first time. The *DNMT3A* mutation (*DNMT3A*mut) in the BM sample from 2013 had a variant allele frequency (VAF) of 31%. In February 2014, cytomorpholocigal BM aspirate analysis indicated the diagnosis of MDS-pCT which can be assumed to be the consequence of a combinational effect of radiation and lenalidomide although there was a considerable time gap between these two therapies.[10] FISH analyses were not performed at that time point. However, retrospective molecular analysis showed a VAF of 35% for the *DNMT3A*mut. In April 2015, chromosome banding and FISH analyses on BM preparations revealed a small clone with a deletion in the long arm of chromosome 20 (del(20q)). For chromosomal analysis, a total of 20 metaphases from BM cultures were analyzed after staining of Giemsa bands. Of these, 18 cells showed a normal female chromosome set (46,XX). The remaining two metaphases showed the del(20q) (46,XX,del(20q)). Interphase FISH analysis revealed the del(20q) in about 3% of cells (Figure 2A). The size of the clone with del(20q) remained stable until April 2016 and had slightly increased to 14% in December 2018. Meanwhile, the *DNMT3A*mut maintained relative stability, hovering around a median VAF of 35%, ranging from 24% to 40% throughout the entire period.

In February 2024, a peripheral blood (PB) sample from the now 80-year-old patient was analyzed, at which time acute leukemia was suspected. Cytomorphological examination of the PB showed 24% undifferentiated blasts in the absence of PC. By FISH on PB smears the previously observed del(20q) was detected in 50% of cells. In addition, a loss of one chromosome X as well as a gain of chromosome 14q identified by an additional signal for the *IGH* locus were detected in 20% and in 13% of interphase nuclei, respectively. Flow cytometry detected a blast population of 35% that was positive for cell surface markers CD19 and CD34, negative for cell surface marker CD10 as well as positive for cytoplasmic TdT, CD22 and CD79a indicating pro-B-ALL. At time of pro-B-ALL diagnosis the VAF of the *DNMT3A*mut was 45%.

To investigate if the MDS-pCT clone transformed into pro-B-ALL or if the pro-B-ALL emerged independently of the MDS-pCT as an additional therapy-related leukemia, interphase FISH with probes for loci on 20q (D20S108 and RH74808/RH67654) and 14q (*IGH*) was performed on the same preparation (Figure 2B). With this approach it was possible to show that there were cells with del(20q) without a copy number alteration for chromosome 14q, but also cells with both aberrations (del(20q) and 14q gain). In contrast, no cells could be detected that harbored only the 14q gain without the del(20q), underpinning the hypothesis of the development of pro-B-ALL from the MDS-pCT clone (Figure 3). Blast counts observed by cytomorphology and immunophenotyping correlated well with the newly identified aberrations (loss of 1 X chromosome (20%) and 14q gain (13%)) while the clone size of the del(20q) which was already detected in the MDS-pCT exceeded the blast fraction in the pro-B-ALL. In addition, a B-cell receptor (BCR) immunoglobulin heavy (IGH) chain fragment analysis had been performed on the pro-B-ALL sample in order to determine BCR clonality. The observed *IGH* status in the pro-B-ALL index clone could not be traced back to the MDS-pCT sample from December 2018, further supporting the development of pro-B-ALL within the MDS-pCT clone.

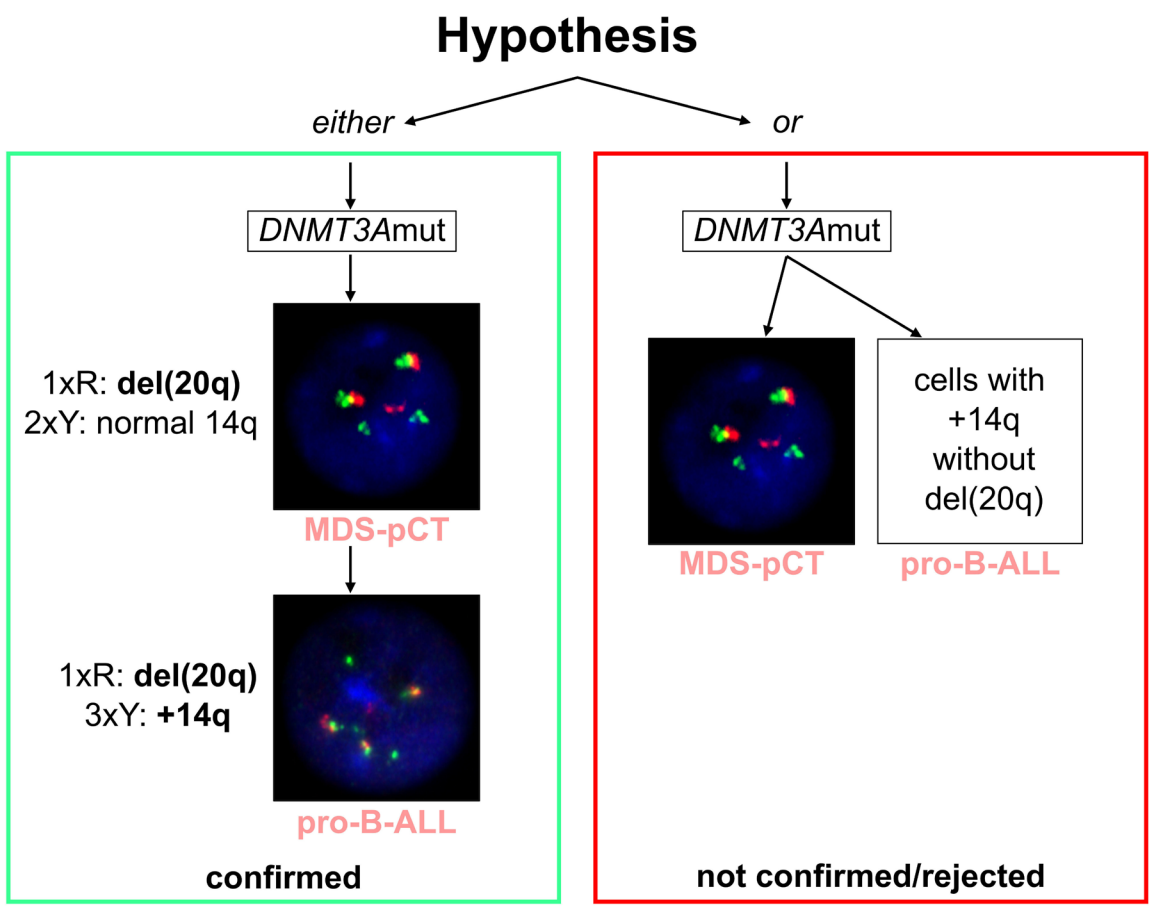

Figure 3. Hypothesis for the development of acute pro-B-cell lymphoblastic leukemia. Initially, 2 possible scenarios were hypothesized to explain the development of pro-B-cell lymphoblastic leukemia (pro-B-ALL). On the left side, a *DNMT3A* mutation (*DNMT3A*mut) is followed by a deletion of chromosome 20q (del(20q)) at the time of myelodysplastic neoplasm post cytotoxic therapy (MDS-pCT) diagnosis. At time of pro-B-ALL diagnosis a gain of 14q (+14q) was aditionally detected. Of note, both aberrations were detected together in cells. On the right side, MDS-pCT and pro-B-ALL developed independently from each other. However, this hypothesis had to be rejected because no cells with +14q but without del(20q) were identified. R: red; Y: yellow.

Unfortunately, the *IGH* status at time of MM diagnosis could not be retrospectively analyzed due to a lack of preserved material making it impossible to make a statement about clonality which would have been of particular interest given the fact of the common B-cell origin of MM and pro-B-ALL. For the same reason, no retrospective molecular genetic analysis could be conducted on samples at MM diagnosis. We can therefore only assume that the *DNMT3A*mut was already present at the time of MM diagnosis as clonal hematopoiesis of undetermined potential (CHIP) which is known to be a precursor lesion for the development of myeloid neoplasms.[11,12] Similarly, Saygin *et al.*[13] were able to show for a patient with *DNMT3A*mut B-ALL that the *DNMT3A*mut was detectable already 6 years prior to the B-ALL diagnosis describing CHIP not only as founder event for the development of myeloid but also lymphoid neoplasms. Furthermore, Morice *et al.*[14] investigated the possible role of lenalidomide as the underlying cause of ALL by conducting a meta-analysis on randomized controlled trials. They observed an increased risk and incidence of secondary ALL in patients with MM who received lenalidomide. Also Geyer *et al.*[15] showed that ALL may arise in patients treated with lenalidomide for MM. Of note, both studies also included patients who had not received chemotherapy with autologous stem cell transplantation. Published data on myeloid and lymphoid neoplasms following treatment for MM typically focus on either secondary MDS/AML or ALL. The unique attribute of the patient presented here, however, is that both MDS-pCT and pro-B-ALL were diagnosed one after another at an interval of 10 years. Through the application of FISH and molecular analyses, we demonstrated that the pro-B-ALL likely developed from the MDS-pCT, instead of arising as a separate, therapy-related leukemia independent of the MDS-pCT.

In summary, this study presents a case of pro-B-ALL in an elderly female patient initially diagnosed with MM and a subsequent MDS-pCT. FISH as well as mutational analyses confirmed the hypothesis that the pro-B-ALL developed from the MDS-pCT clone with a high level of confidence. To the best of our knowledge this is the first reported case on a patient with ALL evolving from MDS-pCT post MM highlighting the need for a nuanced understanding of the risks associated with cancer treatments especially with respect to long-term outcomes such as secondary malignancies.

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Disclosures

WK, TH and CH disclose part ownership of Munich Leukemia Laboratory (MLL). JW, MT, CB and MM are employed by MLL.

Contributions

JW, MT, CB and MM performed research and data analyses. JW wrote the manuscript. WK, TH and CH supervised the study. All authors read and contributed to the final version of the manuscript.

Data-sharing statement

Original data are available upon request in accordance with applying data protection rules.

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