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LETTER TO THE EDITOR

Mixed phenotype acute leukaemia with monosomy 7 and *BCR-ABL1* translocation following antimetabolite therapy for intrahepatic cholangiocarcinoma

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Dear Editor,

A 64-year-old gentleman, who had been diagnosed with intrahepatic cholangiocarcinoma 3 years back and was in remission following resection and adjuvant chemotherapy with a combination of 5-fluorouracil (5-FU) and gemcitabine, presented to us with shortness of breath and weakness for 2 weeks. On examination, he had hepatosplenomegaly. Complete blood count revealed anaemia (Hb 8.5 g/dL), thrombocytopenia (39×10^9/L) and leucocytosis (63.9×10^9/L). Peripheral blood smear and bone marrow aspirate revealed 65% and 78% blasts, respectively. Intriguingly, there were two morphologically distinct population of blasts. The larger blasts (3–3.5 times the size of mature lymphocytes) had opened-up chromatin and prominent nucleoli while the smaller blasts had condensed chromatin with indistinct nucleoli. On cytochemistry, only the larger blasts were positive for myeloperoxidase stain (Fig. 1A). On flow cytometry, a single population of precursor cells were identified which showed simultaneous expression of both myeloid (CD13, CD33, CD117, myeloperoxidase) and B-cell lineage (CD10, CD19, cytoplasmic CD22 and cytoplasmic CD79a) markers (Fig. 1B–G), thereby establishing the diagnosis of mixed phenotype acute leukaemia. Monosomy 7 and *BCR-ABL1* translocation were identified on fluorescence in-situ hybridisation (Fig. 1H–J). Reverse transcriptase polymerase chain reaction (RT-PCR) corroborated the presence of *BCR-ABL1* translocation with p190 transcript (Fig. 1K).

Therapy-related myeloid neoplasm (t-MN) is a recognised entity in the WHO 2016 classification. Recently, there has been much interest in unravelling the drivers of therapy-related lymphoid neoplasm which has been reported to comprise 9–13% of all therapy-related leukaemias. Current evidence suggests that t-ALL arises de novo as an effect of genotoxic therapy, and inherited cancer susceptibility genes play a role in only a small subset of patients [1]. Therapy-related mixed phenotype acute leukaemia (t-MPAL) is an even rarer entity and has been described only in prior case reports [2–8]. The origin, incidence, cytogenetic aberrations, biology and prognosis of t-MPAL remains unexplored because of the rarity of this entity. The exact phenotype profile (B/myeloid versus T/myelod and biphenotypic versus bilineal t-MPAL) is also not known. To the best of our knowledge, this is the first report of the development of B/myeloid MPAL following chemotherapy with antimetabolites (5-FU and gemcitabine) for intrahepatic cholangiocarcinoma.

The occurrence of therapy-related leukaemias after alkylating agents and topoisomerase II inhibitor therapy is well known. The latent period post-exposure to chemotherapy is prolonged with alkylating agents (5–10 years) and shorter following topoisomerase II inhibitors (1–5 years). Therapy-related leukaemias secondary to antimetabolites have been well documented although their incidence remains undetermined. The biology, cytogenetic and molecular profiles of these neoplasms are also underexplored. Our patient developed t-MPAL 3-years after treatment with 5-FU and gemcitabine which is consistent with the relatively short latency that has been previously reported with therapy-related leukaemias post-exposure to 5-FU based antimetabolite therapies [9–11].

Unbalanced chromosomal aberrations like monosomy 7 are common after therapy with alkylating agents while topoisomerase II inhibitors lead to balanced translocations including t(9,22)(q34;q11.2). Presence of Philadelphia chromosome i.e., t(9,22)(q34;q11.2), is a poor prognostic feature in MPAL regardless of the presence of other cytogenetic abnormalities.

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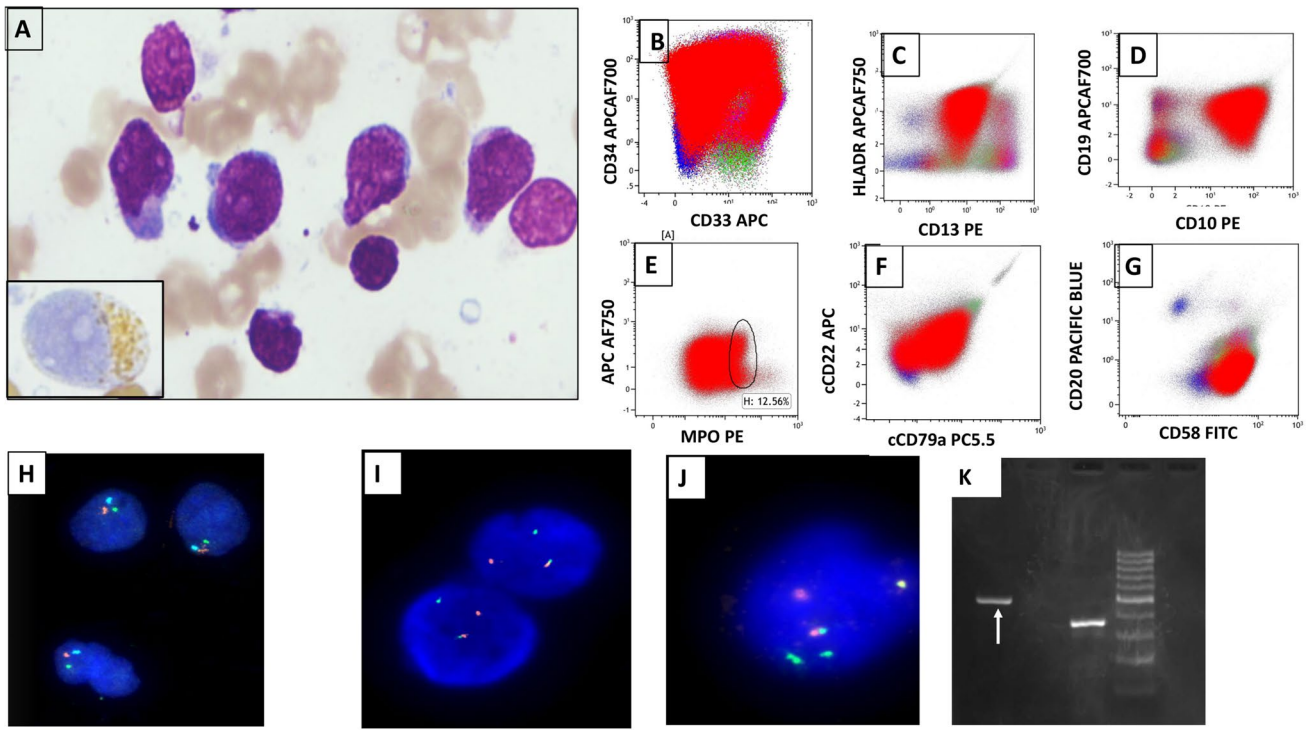

Fig. 1 **A**: Bone-marrow aspirate showing two morphologically distinct populations of blasts; May-Grünwald-Giemsa stain × 100X. (Inset): A large blast shows cytoplasmic staining for myeloperoxidase; **B–G**: flow cytometric immunophenotyping of the gated precursor cells showing positivity for CD34, CD33, CD13, HLA-DR, CD10, CD19, MPO (partial), cytoCD79a, cytoCD22, CD58, negative for TdT (not shown); **H**: FISH using tricolour probe for chromosome 7 reveals monosomy 7; **I**: FISH using *ABL1* break-apart probe shows *ABL1* translocation; **J**: FISH using *BCR-ABL1* dual-colour, dual-fusion probe shows *BCR-ABL1* translocation; **K**: 2% agarose gel of RT-PCR products reveals p190 isoform (521 bp) of *BCR-ABL1* fusion gene in the patient sample (arrow)

Monosomy 7 has also been described in around 10% patients with MPAL. However, the concurrent presence of a t(9;22)(q34;q11.2) and monosomy 7 is rare in MPAL. There is little data on the cytogenetic and molecular aberrations of t-MPAL [2–8]. To the best of our knowledge, this is the first report of the concomitant presence of monosomy 7 and *BCR-ABL1* in t-MPAL.

Author contribution DR: data collection and review, drafting of manuscript; SN: data collection, review of manuscript and final drafting; SS: data collection and critical review of manuscript; NS: data collection and critical review of manuscript; All authors approved the final version of the manuscript.

Declarations

Competing interests The authors declare no competing interests.

References

1. Saygin C, Kishtagari A, Cassaday RD, Reizine N, Yurkiewicz I, Liedtke M et al (2019) Therapy-related acute lymphoblastic leukemia is a distinct entity with adverse genetic features and clinical outcomes. Blood Adv 3:4228–4237
2. Whittle SB, Punia JN, López-Terrada D, Gaikwad A, Hampton OA, Heczey A (2017) Therapy-related acute leukemia with mixed phenotype and Novel t(1: 6)(q25;p23) after treatment for high-risk neuroblastoma. J Pediatr Hematol Oncol 39(8):e486–e488
3. Yang D, Cho SR, Jung S, Lee W, Hwang HY, Lee HS et al (2017) A case of therapy-related acute leukemia with mixed phenotype with BCR-ABL1 after treatment of diffuse large B-cell lymphoma. Ann Lab Med 37:166–168
4. Gong X, Yan L, Xiao X, Tang Q, Zhao X (2018) Secondary mixed phenotype acute leukemia following chemotherapy for diffuse large B-cell lymphoma: a case report and review of the literature. Int J Clin Exp Pathol 11:3104–3110
5. Yamamoto K, Sada A, Kawano Y, Katayama Y, Shimoyama M, Matsui T (2010) Therapy-related, mixed phenotype acute leukemia with t(1;21)(p36;q22) and RUNX1 rearrangement. Cancer Genet Cytogenet 201:122–127
6. Briasoulis E, Tzouvara E, Tsiara S, Vartholomatos G, Tsekeris P, Bourantas K (2003) Biphenotypic acute leukemia following intensive adjuvant chemotherapy for breast cancer: case report and review of the literature. Breast J 9:241–245
7. Cho JH, Hur M, Moon HW, Yun YM, Ko YS, Kim WS et al (2012) Therapy-related acute leukemia with mixed phenotype and t(9;22)(q32;q11.2): a case report and review of the literature. Human Pathol. 43:605–609
8. Bacchiarri F, Sammartano V, Santoni A, Raspadori D, Zappone E, Defina M et al (2021) First reported case of secondary mixed

phenotype acute leukemia after multiple myeloma. Am J Blood Res 11:123–131
9. Pinczés L, Molnár S, Telek B, Illés Á (2018) A case of therapy-related acute myeloid leukemia following treatment with 5-Fluorouracil. Cureus 10:e3769
10. Shapiro S, Hughes G, Al-Obaidi MJ, O'Reilly E, Ramesh S, Smith J et al (2007) Acute myeloid leukaemia secondary to treatment with capecitabine for metastatic colorectal cancer. Eur J Haematol 78:543–544
11. Park HJ, Choi JH, Lee KA, Kim HC, Nam YS, Oh YH et al (2012) A case of therapy-related acute myeloid leukemia following 5-fluorouracil chemotherapy. Korean J Intern Med 27:115–117