

# Discordant end of induction bone marrow morphology and flow cytometry in a paediatric patient with acute myeloid leukaemia

Breanna Breeding, Kelly Ann Bush, Dennis John Kuo 

Division of Pediatric Hematology-Oncology, University of California San Diego, School of Medicine, La Jolla, California, USA

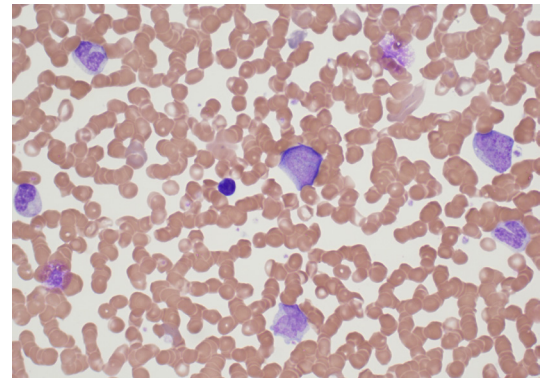
## Correspondence to

Dr Dennis John Kuo;  
dekuo@ucsd.edu

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## DESCRIPTION

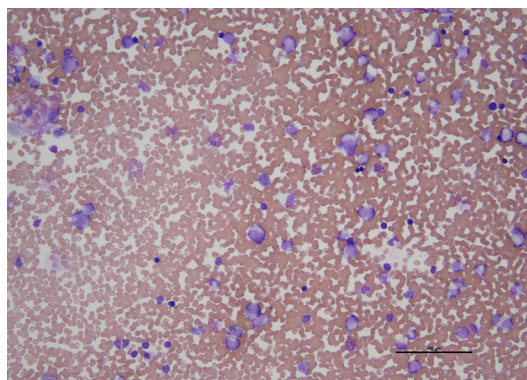
The patient was a 5-year-old boy with newly diagnosed acute myeloid leukaemia (AML) who completed induction 1 chemotherapy on Children's Oncology Group (COG) study AAML1831 arm B with liposomal daunorubicin and cytarabine, and gemtuzumab ozogamicin. Having had a clinically uncomplicated course, on day 31 of cycle 1 he underwent bone marrow aspiration and biopsy with minimal residual disease (MRD) by flow cytometry to assess the response. Peripheral counts recovered after nadir, with an absolute neutrophil count of 341 on day 31. We were notified by pathology several hours after the procedure that his bone marrow aspiration was concerning for 33% myeloid blasts by morphology (figures 1 and 2). This was significantly higher than the 23% blasts seen by morphology at diagnosis and therefore raised concerns for induction failure. Given the apparent lack of response, and our desire to be fully transparent with the family, the treating team reported these results to the parents as soon as they were available, while still awaiting MRD results. During that time plans for an immediate continuation into induction 2 with plans for eventual haematopoietic stem cell transplant were also discussed, which greatly distressed the grieving family. The flow cytometry MRD results returned 3 days later, and no blasts were detected at the threshold of the test ( $<0.02\%$ ). While these results were a great relief to the appreciative family, it was a harrowing 3 days of grief and anxiety. The patient ultimately completed AML chemotherapy and all subsequent



**Figure 2** Bone marrow aspiration smear at 600 $\times$  showing the morphology of immature cells concerning for blasts.

bone marrow evaluations have remained negative by both morphological examination and MRD flow cytometry.

It can be difficult to distinguish leukaemic myeloblasts from benign immature cells in a recovering bone marrow by morphology alone, and the traditional morphological blast percentage of 5% defining remission may be too imprecise when compared with simultaneously performed flow cytometry MRD testing. In a COG report of 12 patients with refractory disease ( $>20\%$  blasts) by morphological evaluation, 1 patient (8%) had no evidence of disease by flow cytometry.<sup>1</sup> A report from St Jude's Children's Research Hospital demonstrated that flow cytometry was markedly superior to morphological review in detecting residual leukaemic disease and in predicting outcome.<sup>2</sup> Of the 1215 samples in remission by morphology ( $<5\%$  myeloblasts), 8.2% were MRD positive ( $\geq 0.1\%$ ) by flow cytometry. More surprisingly though, 57.5% of the 167 bone marrow samples that were not in remission by morphology ( $\geq 5\%$



**Figure 1** Bone marrow aspiration smear at 200 $\times$  showing many immature cells concerning for blasts in a background of normal trilineage maturing haematopoietic cells.



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## Patient's perspective

Hearing that the chemo didn't work was far worse news than receiving the original diagnosis. We were in utter despair. Getting the news a few days later that the MRD was negative was thrilling, but we were left with an uneasy feeling of mistrust in our doctors and the treatment. Luckily we had a meeting with the team and were able to resolve and repair the negative feelings. – Patient's mother

## Learning points

- ▶ Distinguishing malignant leukaemic blasts from benign immature cells in a recovering bone marrow in AML at the end of induction 1 chemotherapy by morphology alone is challenging.
- ▶ Flow cytometry-based minimal residual disease (MRD) testing performs better than morphological review in assessing response to chemotherapy in AML and predicting treatment outcome.
- ▶ Even patients who appear not to be in remission by morphology at the end of induction may be MRD negative by flow cytometry.

blasts) were MRD negative by flow cytometry. In this study, outcomes were most highly correlated with flow cytometry MRD results. By contrast, morphological remission after induction 1 was not associated with better survival. If flow cytometry MRD testing is the gold standard for determining remission, morphological review produces significant percentages of false positives and false negatives and is a poor predictor of survival. Conveying the knowledge of the imprecision of morphology as a measure of treatment response to the family, even when

discussing the apparently concerning morphological findings, could have avoided significant unnecessary distress while they awaited the flow cytometry MRD results.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

**ORCID iD**

Dennis John Kuo <http://orcid.org/0000-0003-4154-0057>

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