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A PEDIATRIC CASE OF TREATMENT-RELATED MYELOYDYSPLASTIC SYNDROME WHILE ON THERAPY FOR PRE-B ALL

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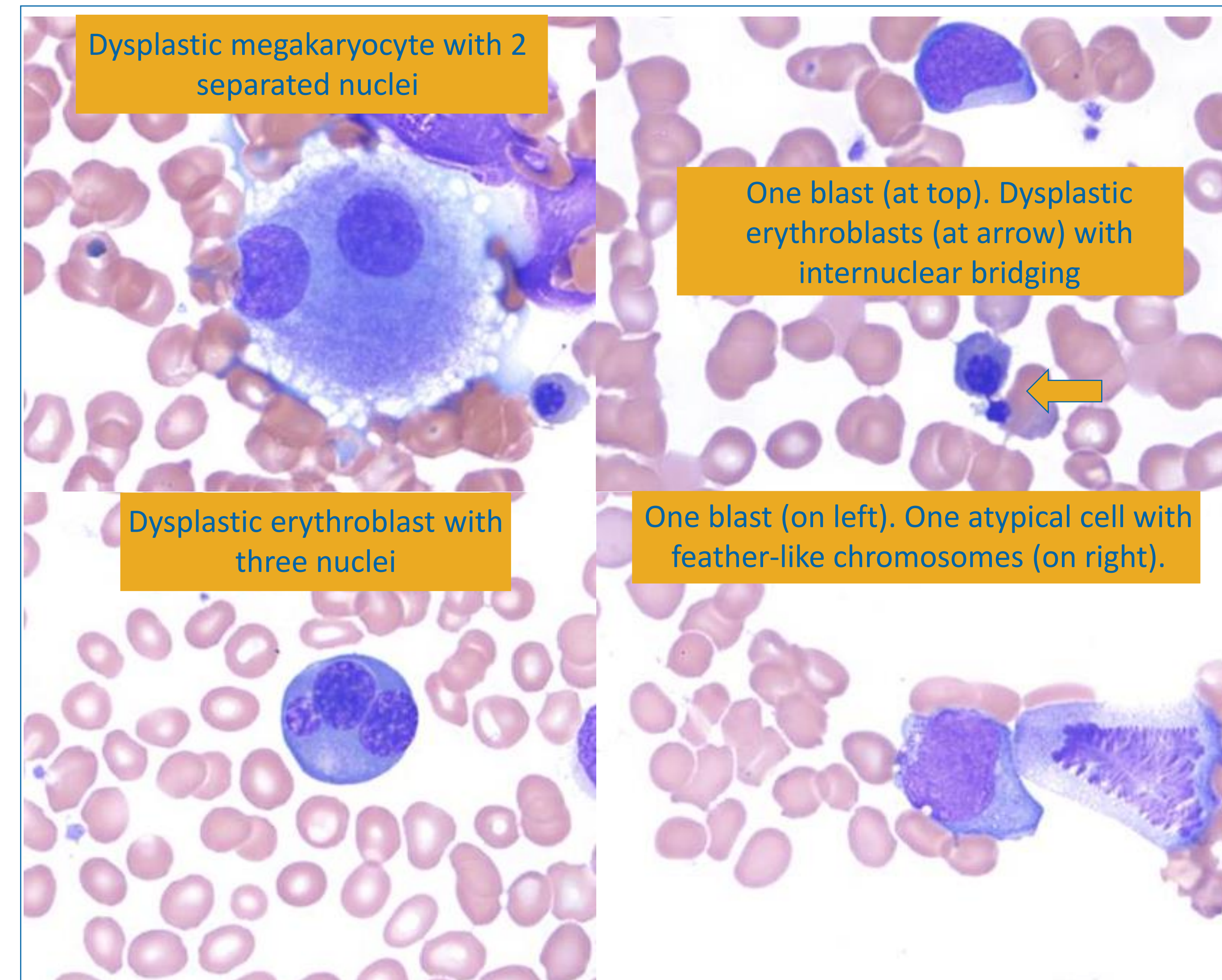
Introduction

- Secondary malignancies, including therapy-related myelodysplastic syndrome (t-MDS) and acute myeloid leukemia (AML), are an uncommon late effect of cancer therapy.
- When t-MDS/AML occurs after treatment with alkylating agents, it is associated with monosomy 5 and/or 7, in contrast to after topoisomerase 2 inhibitors which is associated with 11q23 translocations.
- Average time to development of t-MDS/AML after alkylating agents is typically 5 to 7 years after receiving therapy.
- Hypomethylating agents prolong overall survival and are approved for use in adults with myeloid malignancies.
- The prognosis of t-MDS/AML is very poor despite stem cell transplant with studies demonstrating 5-year survival rates <25%.

Case Description

- The patient is a 17-year-old Hispanic male who was diagnosed with high risk pre-B ALL (CNS2) and received a standard 4-drug induction with negative MRD by flow cytometry at the end of induction.
- The patient received the standard high-risk arm of AALL1131 and a total dose of 3000 mg/m² cyclophosphamide.
- During cycle 6 of maintenance therapy, a routine CBC had 2.8% blasts.
- A bone marrow aspirate (see Images) demonstrated severe erythroid and megakaryopoietic dyspoiesis with 13% myeloblasts by flow cytometry. There was no abnormal immature B-cell population.
- Chromosome analysis showed a reciprocal t(3;3)(q21.3;q26.2); GATA2, MECOM translocation with monosomy 7, consistent with a diagnosis of t-MDS.

Pathology Images



Clinical Course

- The patient completed 4 cycles of azacitidine (hypomethylating agent), prior to transplant. The peripheral blast count cleared after completion of all 4 cycles of azacitidine and the blast percentage in his marrow decreased to 2%.
- Fludarabine, busulfan, melphalan, and rabbit ATG were given as myeloablative conditioning for haplo-identical allogeneic bone marrow transplant.
- The patient received a CD34-selected, T-cell-depleted transplant. On Day +30 his marrow was negative for disease by flow cytometry and cytogenetics.
- On day +60 post-transplant we initiated decitabine maintenance therapy to prevent relapse. The patient completed 6 cycles of decitabine. Follow-up marrow evaluations after 2, 4, and 6 cycles have demonstrated no evidence of myelodysplasia or leukemia.

Discussion

- This patient developed t-MDS while receiving therapy for pre-B ALL, 2 years after his initial dose of cyclophosphamide.
- This case demonstrates a much more rapid development of t-MDS than is expected after treatment with cyclophosphamide and monosomy 7 cytogenetics.
- Hispanics have a higher incidence of t-MDS/AML compared to other racial groups which may have been a factor in the early development of disease.
- Adult and pediatric studies have shown that treatment with hypomethylating agents prior to transplant can reduce blast percentages and decrease risk of relapse. This was demonstrated in this case, with the patient's blast percentage decreasing from 13% at diagnosis to 2% after 4 cycles of azacitidine.
- Patients with t-MDS/AML are at high risk of post-transplant relapse and >70% will relapse at 20 months post-transplant.
- Adult data suggests that maintenance therapy after transplant with hypomethylating agents reduce early relapse, but there is little to no data in pediatrics. This patient remains in remission 10 months post-transplant.

Conclusions

- Alkylating agents are a known cause of t-MDS/AML. This case demonstrates a rare instance of t-MDS developing on-therapy.
- Hypomethylating agents should be considered in patients with t-MDS prior to transplant, to limit additional chemotherapy in already heavily-treated patients.
- Maintenance therapy with hypomethylating agents post-transplant should be considered in patients at high risk of relapse.
- Further studies are needed among pediatric patients to validate the use of maintenance therapy with hypomethylating agents post-transplant to decrease the risk of relapse.

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References available upon request

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