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Title	Mixed Phenotype Acute Leukaemia with KMT2A amplification: A case series study and review of literature
Authors	Ka Ngai LAU[1], Ting Hon Stanford LI[2], Ka Yan NG[2], Wai Shan WONG[2], Coty CHEUNG[3], Natalie Pui Ha CHAN[3], Joyce Sin CHEUNG[3], Wing Kit LAM[1], Alice Ching Ching WONG[1], Sze Fai YIP[1]
Institutions	[1]Department of Clinical Pathology, Tuen Mun Hospital [2]Department of Pathology, Queen Elizabeth Hospital [3]Department of Anatomical and Cellular Pathology, Princes of Wales Hospital

Abstract

Introduction: Gene amplification is rare in Acute Myeloid Leukaemia (AML) and is usually manifested as double minutes (dmin) or heterogeneously staining region (hsr) cytogenetically. Commonly amplified genes include MYC and KMT2A in AML. Previous studies established that AML with KMT2A amplification is a rare distinct disease subtype different from AML with KMT2A rearrangement. It is characterized by morphological dysplasia, highly complex karyotype and is associated with frequent TP53 deletions/mutations and dismal clinical outcomes. Rare case reports of B-lymphoblastic leukaemia with KMT2A amplifications were reported. However, Mixed Phenotype Acute Leukaemia (MPAL) with KMT2A amplifications at diagnosis have not been reported in the literature.

Method: We reviewed and reported the clinicopathological findings of 3 MPAL cases with KMT2A amplification. They all had cytogenetic studies, fluorescence in situ Hybridization (FISH) for KMT2A and myeloid panel next generation sequencing (NGS) performed at diagnosis. FISH for MYC was performed in 2 cases.

Results: We identified 2 male patients and 1 female patients with a median age of 60. None of the patients had history of malignancy nor received chemotherapy or radiotherapy. 2 patients were diagnosed with MPAL, B/Myeloid and 1 patient had MPAL, T/Myeloid. 2 patients had mild prolongation of prothrombin time (PT) at presentation. One of them developed significant coagulopathy with both prolongation of PT and activated partial thromboplastin time during salvage chemotherapy. She developed massive intracranial haemorrhage requiring ICU admission. All cases showed blasts containing cytoplasmic vacuoles and morphologic dysplasia with the presence of hypogranular and hypolobated neutrophils. Complex karyotypes were demonstrated by cytogenetic studies in all cases. 2 cases showed deletion of 5q. FISH for KMT2A demonstrated KMT2A amplification (>5 copies) in all cases. 1 case showed concomitant MYC amplification (>5 copies), and another showed gain of MYC (3 copies). All cases harboured TP53 mutations. The 3 patients all underwent HyperCVAD induction chemotherapy. They all had primary refractory disease and subsequently received either FLAG-IDA, inotuzumab or FLAG as salvage chemotherapy. None of them achieved remission and succumbed with a mean overall survival of 82 days.

Discussion: Our cases of MPAL with KMT2A amplification demonstrate similar clinicopathological features as AML with KMT2A amplification. A novel finding of concomitant gain or amplification of MYC is seen in 2 of the MPAL cases and this warrants further study. Novel therapy is needed for this distinctively rare subtype of leukaemia.

References

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