

Leukaemia Section

Review

Mixed phenotype acute leukemia (MPAL)

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Abstract

Mixed phenotype acute leukemia (MPAL) accounts for 2-5% of all acute leukemias (Weinberg OK et al., 2010). The World Health Organization (WHO) classification of hematopoietic and lymphoid tumors proposed a simpler diagnostic algorithm, which relies on fewer and more lineage-specific markers to define MPAL. MPAL with t(9;22) and MLL rearrangement are now separate subtypes of MPAL and considered as distinct entities (Weir EG et al., 2010). Recent molecular studies demonstrates frequent epigenetic regulatory genes and tumor suppressor genes frequently present in MPAL.

KEYWORDS

Mixed phenotype acute leukemia; World Health Organization

Clinics and pathology

Disease

Mixed phenotype acute leukemia (MPAL) is a rare disease and historically has been labeled by a variety of names including mixed lineage leukemia, bilineal leukemia and biphenotypic leukemia (Weinberg OK et al., 2010). Similar to other acute leukemias, patients with MPAL present with fatigue, infections, bleeding disorders and high number of circulating blasts (Weir EG et al., 2010).

Epidemiology

Mixed phenotype acute leukemia is a rare disease and comprises 2-5% of all acute leukemias. A simpler diagnostic algorithm is now used to define mixed phenotype acute leukemia (MPAL) is used by the World Health Organization (WHO) (Borowitz MJ et al., 2008; Arber DA et al., 2016).

Pathology

Morphologically, blasts in MPAL are mostly medium sized with fine chromatin and indistinct to prominent nucleoli; however these blasts can show classical lymphoid features and appear smaller in size with very high nuclear to cytoplasmic ratios and variably condensed nuclear chromatin, or myeloid features with cytoplasmic granules, very fine nuclear chromatin and large prominent nucleoli. The diagnosis of MPAL rests on the immunophenotypic features of these blasts rather than morphology and flow cytometry is the preferred method for diagnosing MPAL.

The WHO classification proposed a simpler diagnostic algorithm to define MPAL, which relies on fewer, more lineage specific markers. Myeloid lineage requires the presence of myeloperoxidase as detected by flow cytometry, immunohistochemistry or cytochemistry or evidence of monocytic differentiation (with at least 2 of the following markers being positive: non-specific esterase cytochemistry, CD11c, CD14, CD64) (Borowitz MJ et al., 2008). T-lineage can be shown with

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cytoplasmic or surface CD3, at least as intense as background reactive T-cells, and multiple antigens are required for B-lineage including CD19, CD79a, CD22 and CD10 (Borowitz MJ et al., 2008). All possible combinations of MPAL can be observed including B/myeloid, T/myeloid, B/T or even rarely B/T/Myeloid (Borowitz MJ et al., 2008). MPAL with t(9;22) and MLL rearrangement have been separated out as distinct subtypes.

In the 2016 revision to the WHO classification, no new entities were defined within this group of leukemias. Although the list of lineage specific markers is unchanged, it is now emphasized that in cases with 2 distinct blast populations each population should meet criteria for B-lymphoblastic leukemia (B-ALL), T-ALL or acute myeloid leukemia but it is not necessary that specific markers are present (Arber DA et al., 2016). It is also now more specifically stated that cases of otherwise typical B-ALL with only low level expression of MPO (without other evidence of myeloid differentiation) should not be classified as MPAL (Arber DA et al., 2016). Furthermore, a specific statement is now included that cases of otherwise typical ALL or AML do not need to meet the strict lineage defining criteria listed for MPAL

Cytogenetics

MPAL with BCR/ABL1 fusion gene

MPAL with t(9;22)(q34;q11.2) or BCR/ABL1 rearrangement is considered as a separate entity (Borowitz MJ et al., 2008; Arber DA et al., 2016). The t(9;22)(q34;q11.2) translocation results in a BCR / ABL1 fusion gene located on the Philadelphia chromosome (Ph), causing a constitutively active BCR/ABL1 tyrosine kinase. Acute leukemia with t(9;22) and blast phase of chronic myeloid leukemia (CML) have very similar clinical presentations and morphologic features and caution should be used when making a diagnosis. Splenomegaly, peripheral leukocytosis due to maturing myeloid precursors and mature neutrophils, absolute basophilia, and a clinical history of CML may support the diagnosis of blast phase of CML with MPAL phenotype (Arber DA et al., 2016). De novo MPAL with BCR/ABL1 rearrangement generally occurs more frequent in older patients. Although most studies found the frequency of MPAL with t(9;22) to be 28-35%, pediatric studies report it to be much lower at 3% (Al-Seraihy AS et al., 2009). Many of these cases show a dimorphic population of blasts, with most showing B and myeloid lineage (Al-Seraihy AS et al., 2009; Killick S et al., 1999).

MPAL with MLL rearrangement

The second most frequent genetic lesion in MPAL includes translocations involving KMT2A (MLL) gene. MLL rearrangement juxtaposes the amino-

terminus of the histone methyltransferase MLL to a variety of fusion partners, with the most common partner gene being AFF1 (AF4) on chromosome 4 band q21.35 in MPAL (Xu XQ et al., 2009). This tends to occur more commonly in children and is more frequent in infancy (Xu XQ et al., 2009). These cases also tend to present with a dimorphic blast population, one resembling lymphoblasts and the other resembling monoblasts. By flow cytometry, the lymphoblasts usually have a CD19-positive, CD10-negative, B-precursor immunophenotype and are frequently positive for CD15. Usually, the flow cytometry identify a separate population of myeloid blasts with monocytic differentiation.

Genes

Information regarding the mutational landscape of MPAL is based on small studies. Yan et al analyzed 31 patients with MPAL and reported that 12 patients (39%) were found to harbor a known mutation (Yan L et al., 2012). These included IKZF1 deletion in 4 patients (all B-myeloid phenotype with evidence of BCR/ABL1 fusion gene), EZH2 in 3 (B- or T-myeloid; one case showing complex karyotype and another showing loss of chromosome 7), ASXL1 in 2 (both B-myeloid), TET2 in one (B-myeloid), and ETV6 and NOTCH1 in 1 patient each (both T-myeloid) (Yan L et al., 2012). No evidence of mutations in CBL, DNMT3A, FBXW7, FLT3, IDH1, IDH2, KIT, NPM1, PHF6, RUNX1, and WT1 were found in Yan's study (Yan L et al., 2012). Tumor suppressors were also frequently mutated (22%).

Whole-exome sequencing in 23 adult and pediatric patients with MPAL demonstrated that 35% patients had mutations in epigenetic regulatory genes (Eckstein OS et al., 2016). DNMT3A was the most common mutation (23%) followed by IDH2 (9%), TET3 (4%) and EZH2 (9%). All of the DNMT3A mutations involved the methyltransferase domain, three of which were missense mutations at Arg882, the hotspot common in AML. DNMT3A occurred in all immunophenotypic subtypes examined

Mutations of DNMT3A and tumor suppressors showed high variant allele frequency (VAF) suggesting that these mutations arise early in disease. 61% patients also had mutually exclusive mutations of activating signaling genes including NRAS, KRAS and NF1 (Gerr H et al., 2010). NOTCH1 mutations were present in 5 of 16 (32%) with T-myeloid and B/T leukemia. Three samples (13%) also had WT1 mutations.

Treatment

As a result of the absence of prospective trials, there is no set therapy for MPAL patients. A few studies compared outcome of MPAL patients with that of matched control ALL or AML groups and most found that MPAL patients did worse than AML or

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ALL (Weinberg OK et al., 2010). In a study of 61 patients, Weinberg et al., found that when compared with 177 patients with acute myeloid leukemia (AML), MPAL patients had better overall survival ($P = .0003$) and progression-free survival ($P = .0001$) (Weinberg OK et al., 2014). However, no difference in overall survival between MPAL and 387 patients with acute lymphoblastic leukemia was present ($P = .599$) (Weinberg OK et al., 2014). For patients with t(9;22)-positive MPAL, a tyrosine kinase inhibitor (TKI) is usually added to treatment (Wolach O et al., 2015). In his review, Wolach et al suggested that the best approach for the non-t(9;22) MPAL patient is to treat with an ALL regimen and consolidate with an allogeneic stem cell transplant if a donor is available (Wolach O et al., 2015). Shimizu H et al., has suggested that allogeneic hematopoietic stem cell transplantation maybe an effective treatment for MPAL patients, especially early in the disease course (Shimizu H et al., 2015).

Prognosis

In the few larger retrospective series of MPAL, the median overall survival is reported to range from 14.8 to 18 months and rate of achieving long term survival in patients with adult MPAL is poor (<20%) (Matutes E et al., 2011; Deffis-Court M et al., 2014). Most of the retrospective case series suggest that the complete remission rates are higher with ALL therapy or an ALL/AML combined regimen than with AML-type therapy (Liu QF et al., 2013; Gerr H et al., 2010).

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