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Short Communication

t(6;9)(p22;q34) DEK/NUP214 in Childhood

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Abstract

Review on t(6;9)(p22;q34) DEK/NUP214 in Childhood, with data on clinics, and the genes involved.

Keywords
DEK; NUP214; Childhood; acute myeloid leukemia; myelodysplastic syndrome

Clinics and pathology

Disease

Acute myeloid leukemias 1238 (AML) and myelodysplastic syndromes (MDS)

Phenotype/cell stem origin

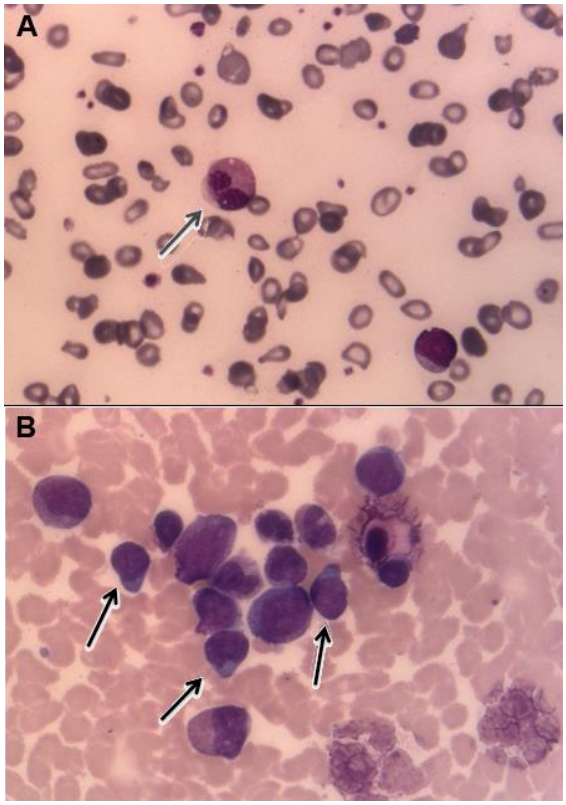
t(6;9)(p22;q34) is a rare subtype of pediatric AML earlier only described in small series and case reports (Gupta, et al 2010, Ishiyama, et al 2012, Slovak, et al 2006). Two large studies both published in 2014 described the clinical, morphologic, and genetic characteristics: the I-BFM-study including 62 children of which 54 was diagnosed as AML and 8 as MDS, and the COG study investigating 48 children all diagnosed as AML (Sandahl, et al 2014, Tarlock, et al 2014). This review is based upon the 110 children from these two series. There are no pediatric studies of stem cell origin. AML in children with t(6;9) is associated with French-American-British (FAB) type M2 (44%) and FAB type M4 (25%) (Sandahl, et al 2014, Tarlock, et al 2014).

Epidemiology

The t(6;9)(p22;q34) was first described in a pediatric patient in 1982 (Kaneko, et al 1982). It is rare, found in only about 1% of all pediatric AML (Sandahl, et al 2014, Slovak, et al 2006, Tarlock, et al 2014) and associated with late onset with a median age 11 years and no patients below 2 years of age (Sandahl, et al 2014, Tarlock, et al 2014). There is an equal sex distribution with 53% males.

Cytology

Basophilia is common in adults with t(6;9). In the I-BFM study, peripheral blood smears from 11 children and bone marrow smears from 15 children with t(6;9)(p22;q34) were evaluable for central review (Sandahl, et al 2014).
All had mild to moderate bilinear dysplasia. Basophils were present in five patients (33%), four of which had 2% basophils, one patient (6%) had 1% basophils, none had > 2%.
From the remaining 47 AML patients, reports on basophils were available in 16 cases; four patients had 1-2% basophils in BM smears, one had 0.4%, and no basophils were reported in the remaining 11. No Auer rods were seen in this reviewed pediatric series. Pseudo-Pelger cells were found in all reviewed material. Furthermore, almost all had tadpole blasts and many have bilobar blasts, both characteristic of AML-M3. However no patients were classified as FAB M3.



BM biopsies from pediatric t(6;9) AML illustrating morphologic characteristics A Pseudo-Pelger-Hüet anomaly tadpole blasts. Illustration from central review by Gitte Kerndrup (2013)

Treatment

It has been suggested that Hematopoietic stem cell transplantation (HSCT) in first complete remission may improve outcome. In the I-BFM-study, the 5-year event-free survival was improved among patients treated the HSCT in CR1 compared with chemotherapy alone (68% vs. 18%; P<0.01) but it did not effect the OS (68% vs. 54%; P=0.48). In the COG study those who received HSCT in CR1 or CR2 had a survival of 60% vs. 21% in those treated with chemotherapy alone (Tarlock, et al 2014).

Prognosis

Complete remission rate is significantly lower compared with pediatric AML patients without t(6;9)(Tarlock, et al 2014), but reported CR rates varied between 67 and 93%. (Sandahl, et al 2014, Tarlock, et al 2014) Furthermore, t(6;9) was associated with high risk of relapse 57%-64%, low 5-year EFS of 32% and 5-year OS around 45%(Sandahl, et al 2014, Tarlock, et al 2014).
The outcome seems better among pediatric t(6,9) patients compared with adults (Slovak, et al 2006).(Ishiyama, et al 2012, Slovak, et al 2006).
Among t(6;9) patients FLT3-ITD had a non-significant negative influence on survival with a 5-year overall survival compared with non-FLT3-ITD (22% versus 62%; p=0.13) in the I-BFM study (Sandahl, et al 2014). The OS in the COG study was in contrast higher with FLT3-ITD than without (40% vs. 27%; p>0.9) which may be explained by FLT3-ITD being allocated to hematopoietic stem cell transplantation (HSCT) (Sandahl, et al 2014, Tarlock, et al 2014)

Genetics

The t(6;9) is often associated with FLT3-ITD reported in 42% to 69% (Sandahl, et al 2014, Slovak, et al 2006, Tarlock, et al 2014).
In the I-BFM study, the gene expression profile was analyzed in 297 pediatric AML patients including eight t(6;9) AML cases. The t(6,9) cases had a significant signature with high expression levels of HOXA and the HOXB (HOXB2, (HOXB3, (HOXB4, HOXB5, HOXB6, HOXB8, and HOXB9) genes described previously (Hollink, et al 2011) but also with high expression of HIST2H4A, PRDM2 (RIZ), SESN1, and EYA3 (Sandahl, et al 2014).

Cytogenetics

Cytogenetics morphological

The translocation is easily detected by conventional karyotyping, only 4/62 pediatric cases were discovered solely by FISH or PCR (Sandahl, et al 2014).

Additional anomalies

t(6;9)(p22;q34) often presents as the sole cytogenetic abnormality (81%). (Gupta, et al 2010). Additional abnormalities are described in 12-19%. (Sandahl, et al 2014) Recurrent aberrations in addition to t(6;9) have been described in 19% with loss of chromosome Y in three boys and trisomy 8 and trisomy 13 each present in three cases, either alone or combined (Sandahl, et al 2014).

Genes involved and proteins

DEK (DEK proto-oncogene)

Location
6p22.3

Protein
375 amino-acids; DEK contains acidic domains (Asp/Glu-rich), a SAF/SAP box, a nuclear localisation signal; and other DNA binding domains. Highly conserved nuclear factor; chromatin remodeling protein, essential for heterochromatin integrity; DEK localizes preferentially at sites proximal to the promoters of expressed genes; acts as a repressor of transcription by interfering with histone acetyl-transferases and as an activator of transcription by stimulating the binding of TFAP2A (the activator protein AP2-alpha) to its target DNA sequences; DEK introduces super-coils into circular

DNA (in Oancea et al., 2010). DEK is a regulator of stem and progenitor cells and is upregulated in a number of neoplasms (breast cancer, chronic lymphocytic leukemia, small cell lung carcinoma, Merkel cell carcinoma, melanoma, glioblastoma, retinoblastoma, cervical, and bladder cancers) (review in Riveiro-Falkenbach and Soengas, 2010); CEBPA and DEK coordinately activate myeloid gene expression (Koleva et al., 2012); DEK is an estrogen receptor alpha (ESR1) target gene (Privette Vinnedge et al., 2012). DEK expression modulates ATM and DNA-dependent protein kinase signaling, and contributes to DNA repair (Kavanaugh et al., 2011).

NUP214 (nucleoporin 214kDa)

Location
9q34.13

Note
The previous name of NUP214 was CAN.

Protein
2090 amino acids; contains dimerization domains (2 leucine zippers) and FG repeats; forms homodimers; the C-terminus is essential; the N-terminus is involved in mRNA export (Köser et al., 2005). Nuclear membrane localisation (cytoplasmic face of nucleopore); component of the nuclear pore complex; involved in nucleo-cytoplasmic transport.

Result of the chromosomal anomaly

Hybrid gene

Description
5' DEK - 3' NUP214 on der(6); head to tail DEK/NUP214 fusion gene (SET/NUP214 exceptional); breakpoint clusters in a single intron of 8 kb (ICB9: 'intron containing breakpoint 9') in NUP214, and in a single intron (of 12 kb) as well (ICB6) in DEK.

Transcript
5.5 kb RNA; no NUP214-DEK reciprocal transcript on chromosome 9.

Detection
RNA-PCR.

Fusion protein

Description
165 kDa; N-term with almost the entire DEK protein fused to the C-terminal two-thirds of the NUP214 protein.

Expression / Localisation
Nuclear localisation.

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