

Leukaemia Section

Review

t(14;19)(q32;p13) IGH/EPOR

t(14;19)(q32;p13) IGH/BRD4 ?

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Abstract

Chromosomal translocations involving the immunoglobulin heavy chain (IGH) locus at 14q32 are common in mature B-cell neoplasms, but infrequent in B-cell acute lymphoblastic leukemia. Among them, the t(14;19)(q32;p13) is a rare but recurrent anomaly described only in a limited number of patients.

KEYWORDS

Chromosome 14; chromosome 19; IGH translocations; B-cell acute lymphoblastic leukemia; t(14;19)(q32;p13); EPOR.

Clinics and pathology

Disease

B-lineage acute lymphoblastic leukaemia (ALL) mainly.

Phenotype/cell stem origin

B-lineage immunophenotype mostly positive for CD10, CD19, CD20, CD22, CD34, CD38, HLA-DR and TdT; may show aberrant expression of myeloid markers, CD13 and/or CD33 (Jaso et al., 2013).

Epidemiology

Rare anomaly, with only 16 cases reported to date; found most often in adolescents and young adults (Table 1).

Among the reported cases there were 9 males and 7 females aged 11 to 74 years (median age 38 years).

13 patients were diagnosed with B-ALL (Micci et al., 2007; Russell et al., 2009; Chapiro et al., 2013; Jaso et al., 2014) and there were sporadic cases of other B-cell neoplasms: 1 chronic lymphocytic leukemia (Finn et al., 1996), 1 splenic marginal zone B-cell lymphoma (Martinez-Climent et al., 2003) and 1 diffuse B-cell lymphoma (Micci et al., 2007).

Table 1: t(14;19)(q32;p13) cases

	Sex/Age Diagnosis	Karyotype	FISH
1.	M/63 CLL	46,XY,t(14;19)(q32;p13)	IGH+
2.	F SMBCL	48,XX,add(1)(p36),+der(1)t(1;17)(p32;q11)t(1;5)(q31;p12),+3,del(10)(p14),t(11;12)(q23;q12),t(14;18)(q32;q21) 47,XX,+der(1)t(1;17)t(1;5)(q31;p11),del(10),t(11;12),t(14;18),t(14;19)(q32;p13)	
3.	16/M B-ALL	46,XY,t(14;19)(q32;p13)	IGH+ BRD4+
4.	36/F B-ALL	46,XX,t(14;19)(q32;p13)	BRD4-
5.	20/20/M DLBCL	50,XY,+X,+add(8)(p11),t(14;19)(q32;p13),+2mar/ 50,idem, t(1;12)(p36;q24)	
6.	F/38 B-ALL	46,XX,t(9;15)(q1?;q1?),t(14;19)(q32;p13)/46,XX,add(9)(p1?),t(14;19)	IGH+ EPOR+
7.	M/11 B-ALL	46,XY,t(14;19)(q32;p13)	IGH+ EPOR+
8.	M/25 B-ALL	46,XY,t(14;19)(q32;p13)	IGH+ EPOR+
9.	M/38 B-ALL	46,XY,t(14;19)(q32;p13)	IGH+ EPOR+
10.	F/60 B-ALL	46,XX,t(14;19)(q32;p13)	No material
11.	F/41	46,XX,t(14;19)(q32;p13)	IGH+ EPOR+
12.	F/38 B-ALL	46,XX,t(14;19)(q32;p13)	IGH+ EPOR+
13.	F/48 B-ALL	39-47,XX,add(5)(q35),del(6)(q23),+add(8)(p23),+11,t(14;19)(q32;p13),-18,-19,+1-4mar	IGH+ EPOR+
14.	M/74 B-ALL	44-45,XY,-4,del(6)(q21),t(14;19)(q32;p13),del(17)(p11)	IGH+ EPOR+
15.	M/21 B-ALL	46,XY,del(12)(p12) at diagnosis 46,XY,t(14;19)(q32;p13) at relapse	IGH+ EPOR+
16.	M/28 B-ALL	46,XY,t(14;19)(q32;p13)	IGH+ EPOR+

Abbreviations: M., male; F., female; CLL., chronic lymphocytic leukemia; SMBCL., splenic marginal zone B-cell lymphoma; B-ALL., B-cell acute lymphoblastic leukemia; DLBCL., diffuse large B-cell lymphoma.). 1. Finn et al., 1996; 2. Martinez-Climent et al., 2003; 3-5. Micci et al., 2007; 6-7. Russell et al., 2009; 8-10. Chapiro et al., 2013; 11-16. Jaso et al., 2014.

Clinics

Patients presented with severe anemia, thrombocytopenia and circulating blasts in B-ALL patients; markedly elevated serum lactate dehydrogenase and serum beta-2-microglobulin levels may be present. Diagnostic bone marrow samples were hypercellular with high blast percentages with a median blast count of 90% (data from Jaso et al., 2013).

Prognosis

Patients with IGH/EPOR fusion described by Jaso et al., 2013 received aggressive multiagent chemotherapy. Among them, 4 of 6 patients achieved an initial complete response, however all developed multiple relapses (median time to relapse was 6 months) and 5 of them died (median survival 12 months). The 38-year-old patient described by Russell et al., 2007 suffered several relapses after diagnosis followed by bone marrow transplant (BMT) 4 months later; she remains alive at 13 months after diagnosis. The second, 11-year-old boy achieved a complete remission, received a BMT 5 months after diagnosis and was alive at 48 months. The outcome of patients described by Chapiro et al., 2013 is known only for the 38 years old male who died 21 months after diagnosis. These data suggest that t(14;19)(q32;p13) IGH/EPOR is associated with an aggressive clinical course and confers a poor prognosis. The 2 remaining ALL patients described by Micci et al., 2007 achieved complete remission; the 16-years old with BRD4 split (see below) remains in remission 27 months and the 36-years old female relapsed after 1 year and died from progressive leukemia 18 months after diagnosis.

Cytogenetics

Cytogenetics morphological

Cytogenetically subtle rearrangement, involving the telomeric end of 14q while the uncertainty of 19p or 19q breakpoints may lead to misinterpretation of breakpoint positions. May resemble the appearance of t(14;19)(q32;q13) with IGH and BCL3 or CEBPA involvements in suboptimal preparations.

Additional anomalies

Described as the sole anomaly in 11 out of 16 cases (Finn et al., 1996; Micci et al., 2007; Russell et al., 2009; Chapiro et al., 2013; Jaso et al., 2014) and found in association with del(6q) in 2,+11 in 1, del(17p) in 1 (Jaso et al., 2014) and in 1 patient it was present in two sidelines (Russell et al., 2009). One patient presented with an initial karyotype of 46,XY,del(12)(p12) and acquired the t(14;19)(q32;p13.1) as the sole abnormality at the time of relapse 39 months later (Jaso et al., 2014). The t(14;19)(q32;p13) was found as a part of complex karyotypes in both lymphoma patients (Martinez-Climent et al., 2003; Micci et al., 2007).

Genes involved and proteins

Note

Involvement of EPOR (Erythropoietin Receptor 4) as the IGH (immunoglobulin heavy locus) partner gene in t(14;19)(q32;p13) has been demonstrated by fluorescence in situ hybridization (FISH) in patients with B-ALL (Russell et al., 2007; Chapiro et al., 2013; Jaso et al., 2013). In 1 patient described by Micci et al., 2007 the IGH was recombined with BRD4 (Bromodomain Containing 4) and in the second case the breakpoint on chromosome 19 was found in a 2.1-Mb region in 19p13.13~19p13.2.

IGH (Immunoglobulin Heavy)

Location

14q32.33

EPOR (erythropoietin receptor)

Location

19p13.2

Protein

Inherited mutations in the erythropoietin receptor causing premature termination of the receptor cytoplasmic carboxy-terminal region have been described in patients with primary familial and congenital erythrocytosis.

BRD4 (bromodomain containing 4)

Location

19p13.12

Protein

Bromodomain-containing protein 4 is a member of the BET (bromodomain and extra terminal domain) family containing 2 bromodomains that recognize epigenetic chromatin modifications, such as acetylated lysine residues. BRD4 plays a role in the maintenance of acute myeloid leukaemia stem cells and is often required for MYC expression, therefore it is possible that deregulated BRD4 expression may lead in sustained MYC expression and aberrant self-renewal (Zuber et al., 2011).

Result of the chromosomal anomaly

Fusion protein

Oncogenesis

B-cell acute lymphoblastic leukemia with t(14;19)(q32;p13), in which IGH and EPOR are juxtaposed, has been reported rarely. The translocation was the sole abnormality in the majority of cases, representing an early, possibly initiating event. Translocations involving the immunoglobulin heavy chain locus results in

juxtaposition with IGH transcriptional enhancers to the partner gene leading to its deregulated expression. EPOR encodes a type I cytokine receptor involved in kinase signaling and is required for normal erythropoiesis. The principal consequence of t(14;19)(q32;p13) is likely over-expression of EPOR, documented by Russel et al., 2007. EPOR is not expressed in normal B-cell precursors and dysregulation of this gene may increase cell survival through activation of the JAK-STAT5. Ectopic expression of EPOR has been identified in B-ALL with t(12;21)(p13;q22) and ETV6 / RUNX1 fusion, indicating that high-level EPOR expression contributes to B-cell precursor transformation by constitutive STAT5 phosphorylation (Dyer et al, 2010; Jasso et al., 2014).

BRD4 split by the t(14;19)(q32;p13) was found only in one of the two examined cases, therefore it is unclear if deregulation of BRD4 or the neighboring NOTCH3 and/or EPHX3 (ABHD9) genes, located distal to BRD4 in 19p13 is implicated in pathogenesis (Micci et al., 2007).

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