

Leukaemia Section

Review

t(X;14)(q28;q11.2) TRA-TRD/MTCP1 / t(X;7)(q28;q34) TRB/MTCP1

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Abstract

T-cell prolymphocytic leukemia (T-PLL) is a rare and aggressive post-thymic lymphoid neoplasm characterized by recurrent chromosome rearrangements that lead to activation of the TCL1A (14q32.1) or the MTCP1 (Xq28) genes. In this report, we focus on the t(X;14)(q28;q11.2), which is thought to occur in approximately 20% of T-PLL cases and leads to overexpression of the MTCP1 gene by relocation to the T-cell receptor alpha/delta (TRA/D) located at 14q11.2 locus. A rare variant of the t(X;14) is the t(X;7)(q28;q34) also leading to overexpression of MTCP1 this time by relocation to the T-cell receptor beta (TRB) locus. Approximately 80% of T-PLL cases, however, are characterized by the inv(14)(q11.2q32.1) and variants, which lead to the activation of the TCL1A (14q32.1) gene by relocation to the TRA/D or TRB gene loci. The additional abnormalities in cases with MTCP1 or TCL1A related abnormalities are similar and include gain of 8q usually in the form of i(8q), as well as deletions 6q, 9p, 11q, and 13q.

Keywords

t(X;14)(q28;q11.2), t(X;7)(q28;q34), T-cell prolymphocytic leukemia (T-PLL), MTCP1, TCL1A, Ataxia Telangiectasia, ATM

Clinics and pathology

Note

These translocations are known to occur in:
T-cell prolymphocytic leukemia (T-PLL)
Ataxia telangiectasia (AT)

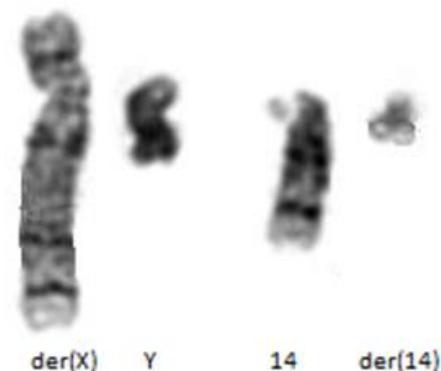
Disease

T-cell prolymphocytic leukemia (T-PLL)

Phenotype/cell stem origin

CD4+CD8- (65-70%) CD4+CD8+ (21-25%), or CD4-CD8+ (10-13%), CD7+ bright and surface CD3 negative in 20% of cases.

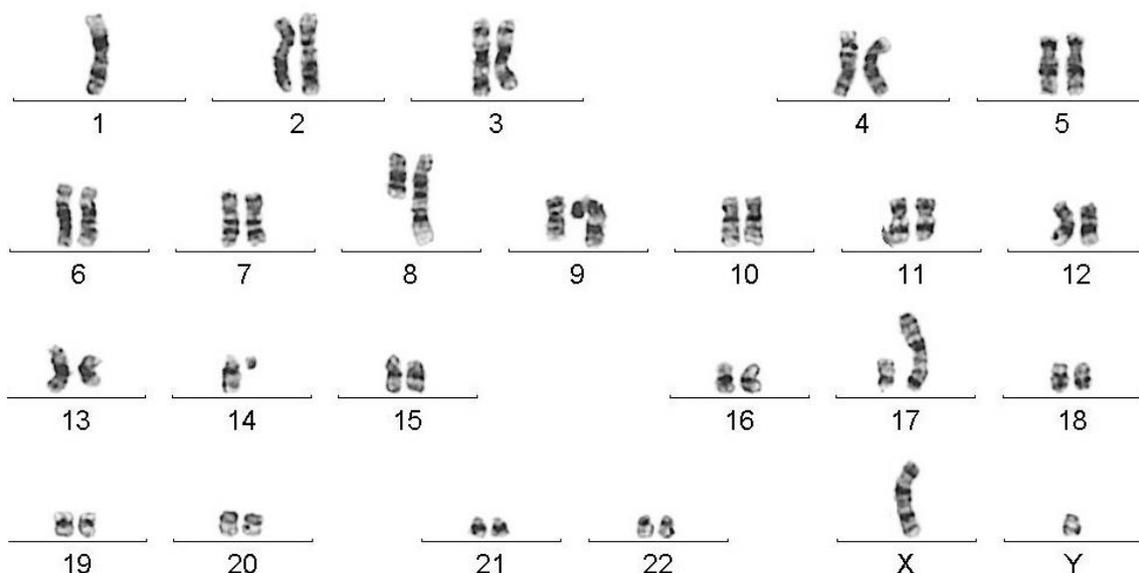
The coexpression of CD4 and CD8 together with weak CD3 and strong CD7 expression suggest that the T-PLL cell stage of differentiation is between a cortical thymocyte and a mature T-cell (Matutes, 1998).



Partial karyotype of the t(X;14)(q28;q11.2)

Etiology

T-PLL accounts for about 2% of all mature lymphoid neoplasms. Most patients are older than 50 years. However, some patients aged as young as 30 years have been reported. The disease affects more male than female patients (3:1 ratio) (Matutes, 1998).



t(X;14) full karyotype.

Epidemiology

The disease is widespread and does not appear to have a geographic predilection or racial clustering.

Clinics

T-PLL is a rare and aggressive post-thymic lymphoid neoplasm characterized by a high white cell count (usually $>100,000/\mu\text{L}$) with associated anemia and thrombocytopenia (Magro et al, 1986). Often there is infiltration of the bone marrow, spleen, liver, lymph nodes, and skin.

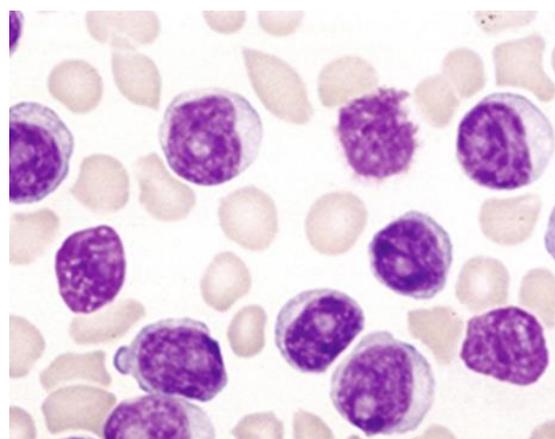
Patients often present with hepatosplenomegaly and generalized lymphadenopathy (Matutes et al, 1991). The median survival is usually ≈ 60 1 year. However, occasional spontaneous remission has been reported in some cases.

Morphologically, T-PLL includes 3 morphologic variants: typical, small cell, and cerebriform, all of which have a similar clinical course and genetic abnormalities (Matutes et al, 1986).

Approximately 15% of patients may be asymptomatic at diagnosis (indolent phase), which might persist several years before progression occurs (Matutes et al, 1998).

Cytology

T-PLL includes 3 morphologic variants: typical, small cell, and cerebriform, all of which have a similar clinical course and genetic abnormalities. Majority (75%) of T-PLL patients have the typical variant where the cells show a regular nuclear outline; 20% have the small cell variant; and 5% have cells with a more irregular nuclear shape similar to the cerebriform cells seen in Sezary syndrome (Costa et al, 2003).



Cytology of typical T-PLL cells in peripheral blood. Cells are medium-sized with regular nuclear outline, single nucleolus, and intense basophilic cytoplasm.

Cytogenetics

Stimulation with a T-cell mitogen (typically PHA) is necessary to obtain metaphase cells for analysis. Most cases of T-PLL have a complex karyotype. Inversion (14)(q11.2q32.1), which leads to juxtaposition of the T-cell receptor TRA/D at 14q11.2 with the TCL1A gene at 14q32.1, is the most common abnormality present in approximately 70% of cases (Costa et al., 2003). Another 10% of patients have the variant t(14;14)(q11.2;q32.1) involving the same genes as the inv(14). Both aberrations lead to overexpression of the TCL1A gene (Mossafa et al., 1994). The t(X;14)(q28;q11.2) is present in about 20% of the cases (de Oliveira et al., 2009). This translocation juxtaposes the TRA/D with the MTCP1 gene at Xq28 and results in overexpression of the MTCP1 gene (Madani et al., 1996; Soulier et al., 1994). Only few cases have been reported with the variant t(X;7)(q28;q34) involving

MTCP1 and the T-cell receptor beta (TRB), which also lead to overexpression of MTCP1 (De Schouwer et al., 2000).

ADDITIONAL ABNORMALITIES Karyotypes are complex in most cases. The most common abnormalities involve chromosome 8, usually as i(8)(q10) in 45% of cases, but also t(8;8)(p12;q11) in 15% of cases, +8 in 15%, and deletion 8p in 15% of cases (Mossafa et al., 1994). Furthermore, frequent losses involving 6q, 9p, 11q, 12p, 13q, 17p/TP53, and 22q, and frequent gains of 6p and 7q have been reported in most complex karyotypes (Matutes et al., 1991; Costa et al., 2003). Mutations in the ATM (ataxia telangiectasia mutated) gene, located in the 11q22.3 region have been associated with inactivation or significantly reduced expression of the ATM protein, which is believed to function as a tumor suppressor (Stankovic et al., 2001).

Treatment

T-PLL is a neoplasm characterized by an aggressive course, poor response to conventional chemotherapy and a short median survival. Treatment with purine analogs and the monoclonal antibody alemtuzumab has resulted in significantly higher response rates and increased survival (Szuszies et al., 2014). However, responses are transient and allogeneic hematopoietic progenitor-cell transplantation remains the only potential curative option. The proportion of patients eligible for transplant is low, owing to the older age group of patients, and nonmyeloablative transplantation is a promising alternative that needs to be explored.

Disease

Ataxia telangiectasia (AT)

Epidemiology

AT onset occurs in early childhood and has an incidence of approximately 1 in 40 000-100 000 live births in the United States. AT is seen among all races and is most prominent among ethnic groups with a high frequency of consanguinity.

Clinics

AT is an autosomal recessive disorder caused by mutations in the ataxia telangiectasia mutated (ATM) gene. Classic ataxia-telangiectasia (A-T) is characterized by progressive cerebellar ataxia beginning between ages one and four years, oculomotor apraxia, choreoathetosis, telangiectasias of the conjunctivae, immunodeficiency, and frequent infections. The disease is included in the group of chromosome instability syndromes associated with an increased risk for malignancy, particularly leukemia and lymphoma. AT children tend to develop B-cell acute lymphoblastic leukemia whereas T-cell acute lymphoblastic leukemia and T-PLL tend to occur in teenager patients.

Various carcinomas are reported to occur in adults. Diagnosis of AT relies on clinical findings, including slurred speech, truncal ataxia, and oculomotor apraxia; neuroimaging; and family history. Laboratory findings that support the diagnosis include: severely depleted levels of intracellular ATM protein, elevated serum alpha-fetoprotein concentration (Swift, 1990).

Cytogenetics

Spontaneous chromatid/chromosome breaks, triradials, quadriradials (less prominent phenomenon than in Fanconi anemia), telomeric associations. The best diagnosis test is on the (pathognomonic) highly elevated level (10% of mitoses) of inv(7)(p14q35), t(14;14)(q11;q32), and other nonclonal stable chromosome rearrangements involving 2p12, 7p14, 7q 35, 14q11, 14q32, and 22q11 (illegitimate recombinations between immunoglobulin superfamily genes Ig and TCR); normal level of those rearrangements are: 1/500 [inv(14)], 1/200 (t(7;14)], 1/10 000 (inv(7)) clonal rearrangements further occur in 10% of patients, but without manifestation of malignancy: t(14;14), inv(14), or t(X;14) (Bartram et al., 1976; Taylor et al., 1992; Thick et al., 1994).

Genes involved and proteins

MTCP1 (Mature T Cell Proliferation 1)

Location

Xq28

Note

The gene has two ORFs that encode two different proteins. The upstream ORF encodes a 13kDa protein that is a member of the TCL1 gene family; this protein may be involved in leukemogenesis (Soulier et al., 1994). The downstream ORF encodes an 8kDa protein that localizes to mitochondria. Alternative splicing results in multiple transcript variants.

DNA/RNA

Complex alternative splicing : two donor sites in exon 1: transcripts A, the most abundant, ubiquitous, splicing from exon 1 to exon 6; transcripts B, rare : splicing from exon 1 to exon 2. Initiation of the transcription : an alternative site of initiation of the transcription in intron 1 has been found in one tumor with a translocation breakpoint in intron 1.

Protein

- p8 MTCP1: coded by transcripts A, 68 amino acids; one domain formed by 3 alpha helices held together by two disulphide bridges in an antiparallel coiled-coil motif.

- p13 MTCP1: coded by transcripts B, 107 amino acids; one domain with a b-barrel topology.

TRA (T cell Receptor Alpha)**Location**

14q11.2

Note

The size of TCR alpha/delta (TRA/D) locus is about 1 Mb. The TRD variable (V) diversity (D) joining (J) and constant region genes are situated within the TRA locus between the TRA V and the TRA J segments. The TRD locus contains three D segments and four J segments, whereas the TRA J region spans approximately 80 Kb and contains at least 61 segments. The TRA/D locus is transcribed in a centromere to telomere direction.

DNA/RNA

The TRD locus contains three D segments and four J segments, whereas the TRA J regions span approximately 80 Kb and contain at least 61 segments. The TRA/D locus is transcribed in a centromere to telomere direction.

Protein

T-cell receptor alpha/delta chain.

TRB (T cell Receptor Beta)**Location**

7q34

Note

The human TRB locus spans 620 kb and consists of 82-85 genes. Enhancers sequences have been characterized at 5.5 kb 3' from TRBC2.

DNA/RNA

The locus contains 2 types of coding elements : TCR elements (64-67 variable genes TRBV, 2 clusters of diversity, joining and constant segments) and 8 trypsinogen genes.

Protein

T-cell receptor beta chain.

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