Peripheral T-cell lymphoma with t(6;14)(p25;q11.2) translocation presenting with massive splenomegaly

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Abstract Recurrent chromosomal translocations associated to peripheral T-cell lymphomas (PTCL) are rare. Here, we report a case of PTCL, not otherwise specified (NOS) with the karyotype 46,Y,add(X)(p22),t(6;14)(p25;q11) and FISH-proved breakpoints in the IRF4 and TCRAD loci, leading to juxtaposition of both genes. A 64-year-old male patient presented with mild cytopenias and massive splenomegaly. Splenectomy showed diffuse red pulp involvement by a pleomorphic medium- to large-cell T-cell lymphoma with a CD2+ CD3+ CD5− CD7− CD4+ CD8+/− CD30− TCRbeta-F1+ immunophenotype, an activated cytotoxic profile, and strong MUM1 expression. The clinical course was marked by disease progression in the bone marrow under treatment and death at 4 months. In contrast with two t(6;14)(p25;q11.2)-positive lymphomas previously reported to be cytotoxic PTCL, NOS with bone marrow and skin involvement, this case was manifested by massive splenomegaly, expanding the clinical spectrum of PTCLs harboring t(6;14)(p25;q11.2) and supporting consideration of this translocation as a marker of biological aggressiveness.

Keywords Peripheral T-cell lymphoma · Translocation · Splenomegaly · IRF4/MUM1 · T-cell receptor alpha · Cytotoxic

Introduction

Peripheral T-cell lymphoma (PTCL) collectively designates a heterogeneous group of neoplasms derived from mature T and natural killer (NK) cells, altogether representing less than 15 % of all lymphomas [1]. These diseases have variable clinical presentation (as predominantly disseminated/leukemic, nodal, or extranodal diseases) and heterogeneous pathological features, but with few exceptions, tend to pursue an aggressive course, and have a poor outcome.

The genetic and molecular aberrations underlying T-cell lymphomagenesis and the biological diversity of PTCL entities remain poorly characterized. Only two entities, namely, anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphoma (ALCL) and T-cell prolymphocytic leukemia (PLL), are characterized by specific chromosomal translocations, involving ALK with NPM1 or other genes, and TCL1 or MTCP1 with TCRAD, respectively [1]. In the past years, a few novel recurrent translocations have been identified in PTCLs, mainly the t(5;9)(q33;q22) leading to SYK/ITK fusion found in association with the so-called follicular variant of PTCL, not
otherwise specified (NOS), translocations involving TP63 and other p53-related genes, and recurrent translocations involving the IRF4 locus in chromosome region 6p25.3, with various partner genes [2–5].

Here, we present the clinical and pathological features of a PTCL, NOS harboring a t(6;14)(p25;q11.2) translocation, juxtaposing the IRF4 and TCRA orientations.

Clinical history

A 64-year-old man with no significant previous medical history presented with complaints of asthenia, fever, arthralgia, dyspnea at rest, and abdominal pain of recent onset (1–2 weeks). At the time of admission, the patient was pale and febrile (38 °C). Physical examination revealed palpable splenomegaly, no peripheral lymphadenopathy, and no skin rash. The white blood cell count was 7,080/mm³, with normal white cell absolute (7.08×10³/mm³) and differential counts, elevated C-reactive protein (CRP) (159.4 mg/L, N=0–6), and increased lactate dehydrogenase (LDH) levels (1,397 IU/L, N=240–480). Liver tests were slightly abnormal with mild elevation of bilirubin levels (11.3 mg/L, N=0–30) and elevated GGT (253 IU/L, N=0–50), while transaminase levels were within normal range. Renal function tests were normal. Serologies for HIV and HCV were negative. An extensive immunological screening was performed in the search of an active infection, but serologies only showed past immunization for Epstein-Barr virus (EBV) and adenovirus.

Computed tomography (CT) of the chest and abdomen confirmed a severe homogenous splenomegaly and normal-sized liver with probable mild steatosis, while no enlarged lymphadenopathy was observed. Given high estimated risk of spontaneous rupture of the spleen, the patient underwent splenectomy on day 9 after admission. Liver needle biopsies were obtained during the same operative procedure.

A diagnosis of PTCL, NOS was rendered (splenectomy, see below). Altogether, including minimal involvement of the liver and bone marrow, clinical staging was stage IVB, international prognostic index (IPI) score was 5, and the prognostic index for T-cell lymphoma (PIT) score was 4. The patient was treated with polychemotherapy (cyclophosphamide, hydroxydoxorubicin, oncovin, prednisone, CHOP) at 3-week intervals. After the fourth course of treatment, the patient developed fever and clinical investigations failed to identify an infectious cause. A bone marrow biopsy revealed diffuse lymphomatous infiltration, and PET showed generalized osteomedullary hyperfixation. The patient’s condition progressively worsened, preventing administration of additional therapy, and he died 4 months after admission with clinically progressive disease.

Pathological findings—methods and results

The spleen measured 25×13×11 cm and weighed 1,495 g. On cut sections, the parenchyma displayed a homogenous beefy red appearance with multiple small subcapsular infarcts (Fig. 1a). No lymph nodes were identified in the hilum. Representative sections were routinely processed for paraffin embedding after B-plus or formalin fixation, according to standard procedures. Microscopic examination showed an overall preserved architecture with pronounced expansion of the red pulp and markedly atrophic white pulp (Fig. 1b–d). The red pulp was overall congested with areas of red blood cell extravasation and hemorrhage and was diffusely infiltrated by atypical lymphoid cells featuring heterogeneous density, distributed mainly in the splenic cords, and sometimes also infiltrating the walls of larger vessels. The lymphoid cells were pleomorphic, medium- to large-sized. The smaller cells had rather round nuclei, while the larger ones had irregular nuclear contours, sometimes lobated nuclei, and variably prominent nucleoli. A few cells had Reed-Sternberg-like features (Fig. 1e). Mitoses were easily seen. There were no significant infiltrate of eosinophils or histiocytes and no granulomas. Upon immunostaining (by the use of a Ventana autostainer for all antibodies, except for TCR gamma stained manually), CD20, CD79a, and PAX5 essentially stained the small residual white pulp nodules (Fig. 1d), while the lymphoid infiltrate in the red pulp was diffusely CD3+ (Fig. 1c, f). The atypical lymphoid cells were CD2+ CD3+ CD4+ CD5– CD7– CD8– CD10– CD19– CD20– CD43+ CD45RA– CD45RO+ CD56– CD57– MUM1+, TCRbeta-F1+, and TCRgamma– and showed an activated cytotoxic profile (TIA1+, granzymeB+) (Fig. 1f–j). In situ hybridization for the EBV (using probes for EBV-encoded RNAs, EBERs) was negative.

The liver biopsy (Fig. 1m) showed mild steatosis and atypical medium to large lymphoid cells within the sinusoids and in some portal tracts, which were positive for CD3 by immunostaining (Fig. 1m, inset) and interpreted as hepatic involvement by lymphoma.

Staging bone marrow aspirate and trephine biopsy were performed. On HE sections, the marrow showed markedly hypercellular trilineal hematopoiesis with complete maturation, and no suspect lymphoid foci; immunostaining for CD3

![Fig. 1 Pathological findings. a Gross appearance of a cut section of the spleen after formalin fixation. b–d Low-power views (original magnification, ×100) of the splenic parenchyma (b, H&E), showing marked expansion of the red pulp by a population of CD3+ cells (c), while the remnants of the white pulp were atrophic (d, CD20). e–l High-power views (original magnifications, ×200 to ×400) of the splenic red pulp, revealing atypical pleomorphic medium- to large-sized lymphoid cells (e, H&E) with the following immunophenotype: CD3+ (f), CD5– (g), TCRbeta-F1+ (h), TIA1+ (i), MUM1+ (j), CD4+ (k), CD8– (l). m High-power view (original magnification, ×400) of the liver biopsy, showing intrasinusoidal atypical CD3+ lymphoid cells (H&E; inset, CD3).](image-url)
highlighted scattered randomly distributed atypical lymphoid cells with irregular hyperchromatic nuclei, mostly isolated or sometimes in small groups. No abnormal lymphoid component was observed on the bone marrow smears. Flow cytometry analysis of the aspirate performed in the hematology laboratory showed a small population of lymphoid cells (5%) coexpressing CD3, CD4, and CD8.

Conventional cytogenetic analysis performed on a spleen tissue sample and on the bone marrow showed the same abnormal clonal karyotype: 46,Y,add(X)(p22),t(6;14)(p25;q11) in 3 of 4 metaphases from DSP30/IL2-stimulated spleen cultures and 4 of 20 metaphases from classical bone marrow cultures (Fig. 2a). The remaining metaphases showed a regular male karyotype 46,XY. Fluorescence in situ hybridization (FISH) studies were performed with break-apart probes for TCRAD (Abbott, Wiesbaden) and IRF4 [6]. A total of 37/100 and 30/100 nuclei counted showed a signal pattern indicating a breakpoint in the TCRAD and IRF4 locus, respectively, demonstrating that both loci were involved in the translocation (Fig. 2b, c). Moreover, fusion of both loci was detected by a double-color double-fusion assay in 30/100 nuclei using breakpoint spanning probes for the TCRAD [7, 8] and IRF4 [6], which confirmed juxtaposition of IRF4 and TCRAD (not shown).

A monoclonal rearrangement of the T-cell receptor gamma gene (TCRG) was evidenced in the spleen and in the bone marrow, with a clonal peak of identical size in both locations.

At progression, the bone marrow trephine biopsy revealed fibro-edema and, despite overall low cellularity, a diffuse infiltration by neoplastic lymphoid cells, with similar

**Fig. 2** Genetic findings. a QFQ-banded karyogram of a representative metaphase showing the following karyotype: 46,Y,add(X)(p22),t(6;14)(p25;q11) (arrows point at derivatives der(6)t(6;14) and der(14)t(6;14)). b Metaphase FISH with a TCRAD break-apart probe showing a colocalized signal for the intact TCRAD locus on the normal chromosome 14, an isolated red signal on der(14)t(6;14), and an isolated green signal on der(6)t(6;14), indicating a breakpoint in the TCRAD locus. c Interphase FISH with an IRF4 break-apart probe showing a split of the red and green signals in the tumor cells indicating a breakpoint in the IRF4 locus, in addition to one intact copy of IRF4 (colocalized red/green signal)
morphology and immunophenotype (CD3+ CD5− CD4+ CD8+/− TIA1+) to those observed at diagnosis. No significant intrasinusoidal pattern was noted.

Discussion

This is the third report of a case of PTCL, NOS associated with a balanced t(6;14)(p25;q11) translocation involving the IRF4 and TCRAD loci (Table 1). The first two cases reported by Feldman et al. had similar clinicopathological features. Both occurred in older men who presented with mild cytopenias and were found to have massive bone marrow involvement by lymphoma, without peripheral blood involvement and without significant lymphadenopathy or hepatosplenomegaly, and both patients developed skin lesions during the course of the disease. The lymphoma cells were medium or medium to large and, in both cases, had a cytotoxic immunophenotype [3]. One of these patients was still alive at 4 months after diagnosis but was experiencing progressive cutaneous disease, while the other was lost to follow-up. Interestingly, the characteristics of the present case partly overlap with those of the princeps cases, bringing support to the notion that IRF4/TCRAD translocations might define a rare subset of PTCL, NOS with distinct clinicopathologic features. PTCLs harboring IRF4/TCRAD translocation are derived from αβ T cells, feature pleomorphic medium- to large-sized cell morphology, and are CD3+ CD5− (2/2 cases tested) double positive for CD4 and CD8 (2/2 cases tested) with a cytotoxic immunophenotype and negative for EBV. Regarding the clinical presentation, while it was suggested that bone marrow and skin involvement was typical of t(6;14)(p25;q11.2)-positive PTCLs, the current case differs by its predominantly splenic involvement and the lack of skin lesions, while the bone marrow infiltration, albeit subtle at the time of diagnosis, progressed under treatment. Interestingly, common to all three cases is the lack of lymph node involvement. The clinical course of our patient clearly reflects an aggressive disease with rapid resistance to chemotherapy ending with fatal outcome. Follow-up information for the cases reported by Feldman et al. is unfortunately incomplete, but in one of these cases, there is documented early disease progression under treatment. It can therefore be suspected that PTCLs with IRF4/TCRAD translocations represent a particularly aggressive subset of PTCLs.

While chromosomal breaks involving the TCR gene loci occur recurrently in lymphoblastic T-cell neoplasms and in T-cell prolymphocytic leukemia, their overall prevalence in PTCL, NOS is extremely low [9]. Nevertheless, like typical for T-PLL and T-ALL with TCRAD translocation, the present case shows leukemic involvement. The rare TCR translocations (mostly involving the TCRAD locus) in PTCL yet remain poorly understood, as the identity of the translocation partner(s) has not been identified in most cases [7, 10, 11]. The poliovirus receptor-related 2 (PVRL2) has been cloned as the partner gene of the TCRAD in the t(14;19)(q11;q13) translocation and appears to be associated with overexpression of both PVRL2 and BCL3 messenger RNAs (mRNAs) [12, 13].

In the case of the t(6;14)(p25;q11.2) translocation discussed here, the question is which gene(s) in chromosome band 6p25 is (are) deregulated by the juxtaposition to TCRAD. MUM1, encoded by IRF4, is strongly expressed in the tumor cells which might indicate IRF4 to be the target. However, other rearrangements of the IRF4 locus at 6p25, unrelated to TCRAD, have been identified in a substantial proportion of ALK-negative ALCLs of the systemic or cutaneous type and have been shown to involve the DUSP22 phosphatase gene located more telomeric to IRF4 [14–16]. IRF4, also known as multiple myeloma oncogene-1 (MUM1), is a transcription factor acting as a regulator of normal lymphoid differentiation. IRF4 expression in normal lymphoid cells is essentially restricted to plasma cells, some B cells, and activated T lymphocytes, while its expression is deregulated in a variety of B- and T-cell neoplasms, including a subset of plasma cell myelomas and B cell lymphomas harboring structural modifications of the gene [6, 17]. ALK-negative ALCLs are usually positive for MUM1 expression, irrespective of 6p25 rearrangements, and no significant difference in the IRF4 mRNA levels has been evidenced between translocated and non-translocated cases [3]. In PTCL, NOS, MUM1 expression has generally been associated with a CD30+ immunophenotype. Given the consistently strong immunoreactivity for MUM1 antibodies in the three cases with IRF4/TCRAD in the absence of CD30 expression, it seems reasonable to infer that the translocation induced deregulated overexpression of the IRF4 gene.

The splenic involvement by this t(6;14)(p25;q11.2)-positive PTCL was characterized by diffuse red pulp expansion, which is the most frequent pattern of splenic involvement by mature NK/T-cell lymphoproliferations [18]. In particular, differential diagnostic considerations in this case include hepatosplenic T-cell lymphoma (HSTL) and splenic involvement by T-cell large granular lymphocytic leukemia (T-LGL), two entities with a cytotoxic phenotype. HSTL tends to occur in young adults and is typically derived from γδ T cells, but αβ variants have been described as well; more divergent from the case reported here are the typically intrasinusoidal distribution of the lymphoma cells, their monomorphic appearance, and their non-activated cytotoxic phenotype in HSTL. In addition, most cases of HSTL are associated with an isochromosome 7q. T-LGL is a usually indolent lymphoproliferation of CD3+ CD8+ cytotoxic T cells in older individuals, comprising a circulating leukemic component and a usually mild splenomegaly [1].
| Case 1 (3) | M/67 | Bone marrow, skin (at progression) | Medium to large cells, pleomorphic | CD3+ CD4+ CD5− CD8+ CD30− TCRbeta-F1+ Cytotoxic, activated | MUM1+ EBV− | 48-49, XY, +3[5], +5, der(6)(p25;q11.2), +16,+16[5],−14,+16,+1-2mar[cp6]/95-98, idemx2,+3-8mar[2] | CHOP, ICE, ITMTX | Alive at 4 months with progressive cutaneous disease |
| Case 2 (3) | M/71 | Bone marrow, skin (at progression) | Medium cells | CD3+ CD5− CD30− TCRbeta-F1+ Cytotoxic | MUM1+ EBV− | 49,XY,+add(3)(q127),t(6;14)(p25;q11.2),+8,+9,+19,+21 | NA | NA |
| Case 3 (current) | M/64 | Spleen, liver, bone marrow | Medium to large cells, pleomorphic | CD2+ CD3+ CD4+ CD5− CD7− CD8+ CD30− CD43+ CD56− TCRbeta-F1+ Cytotoxic activated | MUM1+ EBV− | 46,Y,add(X)(p22),t(6;14)(p25;q11.2) | CHOP | Progressive bone marrow disease under treatment, died of disease at 4 months |

*CHOP* cyclophosphamide + hydroxydoxorubicin + oncovin + prednisone, *ICE* ifosfamide + carboplatin + etoposide, *ITMTX* intrathecal methotrexate, *NA* not available
In summary, the case reported here expands the clinical spectrum of PTCLs harboring t(6;14)(p25;q11.2) and supports consideration of this translocation as a marker for a subset of clinically aggressive cytotoxic PTCL. Collection of additional cases will be necessary to clarify their pathobiology. This report also expands the differential diagnosis of cytotoxic T-cell lymphomas with predominantly splenic involvement.

Conflict of interest  We declare that we have no conflict of interest.

References