An oligonucleotide arrayCGH approach of primary cutaneous CD30+ anaplastic large cell lymphomas

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Introduction

The clinical and histological features of primary cutaneous CD30-positive anaplastic large cell lymphoma (C-ALCL) have been well characterized, but little is known about its underlying pathogenetic and genetic alterations. Previous comparative genomic hybridization (CGH)[1-5] and array CGH (aCGH)[2,6,7] studies focused on C-ALCL have obtained non-homogeneous results.

Aim

To analyze genetic abnormalities of C-ALCL using a 60-mer 44K oligonucleotide-array-CGH platform and to relate the results with the observed clinical features and previous studies.

Patients and Methods

An EORTC multicenter study was conducted in the departments of Dermatology and Pathology in six different centers of Spain and Switzerland.

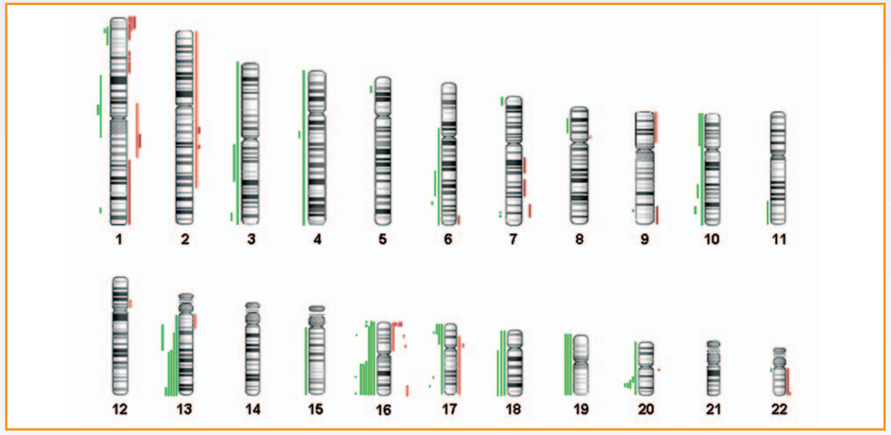
Nineteen patients diagnosed of C-ALCL according to the WHO-EORTC classification for cutaneous lymphomas criteria were selected.

DNA was isolated from 20x10 μm snap frozen samples. Genome-wide analysis was conducted using the Human Genome CGH 44K microarrays (G4410B and G4426B) (Agilent Technologies, Palo Alto, CA, USA). Fluorescence in situ hybridization (FISH) with non-commercial probes of bacterial artificial chromosome (BAC) DNA clones from the CHORI BAC/PAC resource was performed to confirm chromosomal abnormalities in cases with available paraffin embedded tissue biopsy.

Results

Chromosomal abnormalities were detected in 17 out of 19 analyzed C-ALCL samples (89.5%), losses being more frequently detected than gains (78.9% vs. 68.4%). Regarding the smallest overlapping regions of imbalance, 15 corresponded to losses and 9 to gains (Figure 1). Deletions were mainly located on 16q12.1, 16q22.1 and 16q24.3 (36.8%), whereas the highest frequency of gains was detected on 16p13.3pter (21%) (Table 1). Genomic losses of 13q34 (*ING1*) and 16q22.11 (*CTCF*) were confirmed by FISH in 3 patients. No significant correlation between the observed clinical features and the presence of chromosomal aberrations was demonstrated. Furthermore, no data regarding the prognostic significance of the observed genetic results was obtained.

Figure 1. Oligonucleotide arrayCGH results. Red lines at the right side represent gains whereas the green lines at the left side represent losses of genomic DNA



Footnote: *Losses on chromosome 19 were not considered in the final analysis due to the difficulties of evaluating chromosomal copy number imbalances.*

Table 1. Minimal common regions altered in C-ALCL patients

GAINS		
Chromosome region	**N, % patients**	**Candidates genes**
16p13.3pter	4 (21%)	Not possible candidate oncogenes
1p36.32pter	3 (15.8%)	*MIB2, SKI, PRDM16*
1p36.31	3 (15.8%)	*PARK7, DFFA, PRDM2*
LOSSES		
Chromosome region	**N, % patients**	**Candidates genes**
16q12.1	7 (36.8%)	*SIAH1,SALL1,RBL2, FTS, BBS2, MT4, CX3CL1, GPR56, NDRG4*
16q22.1	7 (36.8%)	*CBFB, TRADD, E2F4, CTCF, THAP11*
16q24.3	7 (36.8%)	*CBFA2T3, ANKRD11*
16q11.2	6 (31.5%)	*IRX5*
16q21	6 (31.5%)	*CDH5, CDH11, CDH16*
16q22.1	6 (31.5%)	*NFATC3, CDH1, DERPC,NQ01, ZNF23, CHST4, ATBF1,ADAMTS18, WWOX, DNCL2B, CDH13, HSBP1, OKL38, WFDC1, FBX031, BANP, IL17C*
16q24.3	6 (31.5%)	*DPEP1, ZFP276, GAS8*
13q33.3	5 (26.3%)	*LIG4, COL4A1, ING1, SOX1, LAMP1*
13q14.3	4 (21%)	Not possible candidate tumor supressor genes
13q21.32	4 (21%)	*DIAPH3, PCDH20, PCDH9, DACH1, SCEL, EDNRB, POU4F1, SPRY2, DNAJC3, ZIC2, ERCC5*
16p13.13	4 (21%)	*LITAF*
16p13.12	4 (21%)	*NDE1*
17p13.1	4 (21%)	*TNK1, CHRNB1, ZBTB4, POLR2A, SAT2, TP53, FLJ10385*
20q13.13	4 (21%)	*CEBPB*

Discussion

As Laharanne et al.[7], our study detected losses more frequently than gains, whereas gains were more frequently found by Mao et al.[2] and van Kester et al.[6] The present study detected the lowest frequency of chromosomal aberrations (36.8%) regarding previous publications. In concordance to van Kester et al. and Laharanne et al., two regions have been found also lost in our study at 13q33.3 and 16p11.2. As van Kester et al., we also found losses at 3p26.3, 6q21, 8p22, 13q12.11, 13q13.1, 16p11.2-16q11.2, 17p13.1, and 17p13.3. The main concordance between our results and those of van Kester et al. was a deletion at 16q11.2. However, differences were observed for a higher frequency of 16q losses in our series.

The most interesting regions of loss were those affecting *CTCF* (16q22.1), *ANKRD11* (16q24.3), *ING1* (13q33.3) and *TP53* (17p13.1) genes, all of them involved in the *TP53* signaling pathway. Moreover, 10/19 (53%) patients displayed one or more defects affecting this pathway, which, in our opinion, seems to be important in the pathogenesis of C-ALCL.

Conclusions

Although a high percentage of C-ALCL patients showed genetic abnormalities in our study, most of them presented a low number of alterations (median 4, range 0 to 16) and there were highly heterogeneous among distinct patients, without a clear recurrent pattern unlike other CTCL. Taking results of the different aCGH studies into account, no characteristic pattern of chromosomal aberrations has so far been defined. Besides, other altered genetic mechanisms not implicating gains or losses of DNA could be involved in the pathogenesis of C-ALCL.

Acknowledgments

This study has been supported by Fondo de Investigación Sanitaria, Spanish Ministry of Health Grants No. PI051827 and No. PI080856, and by the Red Temática de Investigación Cooperativa en Cáncer Grants No. RD07/0020/2004, RD06/0020/0076 from Spanish Ministry of Science and Innovation, FEDER.

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