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Short communication

Comparative genomic hybridization identifies 17q11.2~q12 duplication as an early event in cutaneous T-cell lymphomas

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Abstract Mycosis fungoides (MF) and Sézary syndrome (SS) are primary cutaneous T-cell lymphomas (CTCL), a heterogeneous group of extranodal non-Hodgkin lymphomas. In the three cases of MF and four of SS studied, comparative genomic hybridization detected chromosomal imbalances in all SS cases and in one MF case. In all five abnormal cases, the long arm of chromosome 17 was completely or partially duplicated; in three of these five cases, it was the sole genomic event. Notably, a minimal common duplicated region at 17q11.2~q12, corresponded to the mapping of HER2/neu and STAT family genes. The only recurrent loss involved chromosome 10, with deletion of the entire long arm in one case and deletion of band 10q23 in another. Sporadic imbalances included gains at chromosome arms 1q, 2q, 7p, 7q, and 12p. Genomic duplication at 17q11.2~q12 emerged as a primary karyotypic abnormality common to both MF and SS, which suggests that this is an early clonal event.

1. Introduction

Among primary cutaneous T-cell lymphomas (CTCL), a heterogeneous group of extranodal non-Hodgkin lymphomas, the most common forms are mycosis fungoides (MF) and Sézary syndrome (SS), which share similar histopathological features and, together, have an annual incidence of 0.29–0.36 per 100,000 in developed countries[1].

An indolent form of cutaneous lymphoma, MF is characterized by diffuse erythroderma, erythrodermic plaques, and a cutaneous tumoral mass (one or more in combination). Sézary syndrome, which may be primary or a disease progression of MF, presents with malignant circulating T-lymphocytes (Sézary cells) and peripheral lymphadenopathy; it is more aggressive than MF, and prognosis is worse [2].

The underlying genetics of these two entities have been explored only in part by conventional cytogenetic studies, because of the low mitotic index of the MF and SS clones and poor morphology of their mitoses. Furthermore, because peripheral blood is not involved in MF, only skin samples can be karyotyped, which is difficult because of terminal differentiation of tumor cells and contamination by a large population of reactive cells. The few studies available have reported 17q duplications as a recurrent genomic aberration in SS [3,4]. Comparative genomic hybridization (CGH) analysis of DNA overcomes the limits of conventional cytogenetics when dividing cells are not available [5–7]. With paraffin-embedded cutaneous biopsies as a source of DNA from patients with MF or SS, our metaphase-CGH approach identified the minimal duplicated region in the 17q duplication.

2. Materials and methods

Three cases of MF and four cases of primary SS at first diagnosis were selected from patients referred to the ''Istituto Dermopatico dell'Immacolata'' in Rome, Italy. Demographic and clinical data are given in Table 1.

Test DNA for CGH analysis was extracted as previously described [8] from paraffin-embedded cutaneous biopsies that had been collected for diagnosis. Reference DNA was extracted from peripheral blood cells of a healthy donor.

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Table 1
Clinicodemographic data and comparative genomic hybridization (CGH) findings for mycosis fungoides (MF) and Sézary syndrome (SS) patients

Case	Sex/Age, yr	Diagnosis	Staging[a]	CGH analysis	
				Gains	Losses
1	F/46	MF	IVa (T3, N3, M0)	—	—
2	F/45	MF	Ib (T2, N0, M0)	1q21~q41, 17q11.2~q22	—
3	M/35	MF	IIb (T1, N0, M0)	—	—
4	F/58	SS	IVb (T4, N3, B1, M1)	2q24~q31, 7p, 7q21, 7q32~qter, 12p, 17q11.2~q12	10q23
5	M/70	SS	IVa (T4, N3, B1, M0)	17q11.2~q23	10q
6	M/45	SS	IVb (T4, N2, B1, M1)	17q	—
7	M/65	SS	IVb (T4, N3, B1, M1)	17q11.2~q22	—

[a] Tumor–node–metastasis (TNM) classification as reviewed by Girardi et al. in 2004 [27].

The CGH experiments were performed using the method of Kallioniemi et al. [9] and El-Rifai et al. [10], with slight modifications. Fluorescence analysis was performed using an Olympus microscope equipped with a cooled charge-coupled device camera (SenSys; Photometrics, Tucson, AZ) and a Vysis SmartCapture digital image analysis system (Abbott Molecular, Des Plaines, IL). Chromosomal regions were considered overrepresented when the corresponding green-to-red ratio was >1.18 and underrepresented when the ratio was <0.83.

3. Results and discussion

CGH analysis was successful in all cases. The four cases of SS and one of the three cases of MF showed an abnormal CGH profile (Table 1). Losses were less frequent than gains (2 losses, both in SS, vs. 11 gains in MF and SS). Losses involved chromosome 10 with deletion of the entire long arm in one case and of band 10q23 in the second. Cytogenetic and molecular genetic studies had already reported the 10q22~q26 region as frequently involved in deletions or unbalanced translocations in MF and SS [5–7,11].

Extensive loss of heterozygosity analysis identified two deleted regions on 10q in MF and SS [12]. The first, 10q23~q24.1, contains many putative tumor-suppressor genes, including *PTEN*, which seem to be associated with progression from plaque to tumor stage in MF [13]. *PTEN* is involved in germline mutations leading to an autosomal-dominant cancer predisposition syndrome [14]. *PTEN* somatic mutations were also reported in lymphoid malignancies, including T-cell acute lymphoblastic leukemia and large B-cell lymphomas [15,16]. Among other genes mapping at 10q23~q24.1 and implicated in the pathogenesis of MF and SS [12], *KIF11*, *HHEX*, and *HELLS* are involved in lymphoid cell proliferation and hematopoietic differentiation.

In the present series, gains involving chromosome regions 1q21~q41, 2q24~q31, 12p, and chromosome 7 were sporadic, even though they have been recognized as recurrent imbalances in MF and SS [7]. The only recurrent genomic gain in the four cases of SS and the one case of MF was 17q duplication (Table 1). In SS, 17q duplications were originally observed by conventional cytogenetic analysis on peripheral blood lymphocytes cultures, stimulated with phytohemagglutinin or interleukin 2 and 7 [3,4]. CGH and fluorescence in situ hybridization (FISH) definitively established 17q duplications in 18–27% of SS [17,18]. Using CGH, Fischer et al. [7] were the first to observe a 17q gain in one case of stage IIb MF. Given that our MF case was at stage 1b and disease was stable, our results show that 17q duplication is present in very early stage MF.

Despite the heterogeneous size of 17q duplications, we were able to identify a small common duplicated region in case 4 (SS) (Fig. 1). Encompassing the terminal portion of band 17q11.2, and band 17q12, the region contains genes

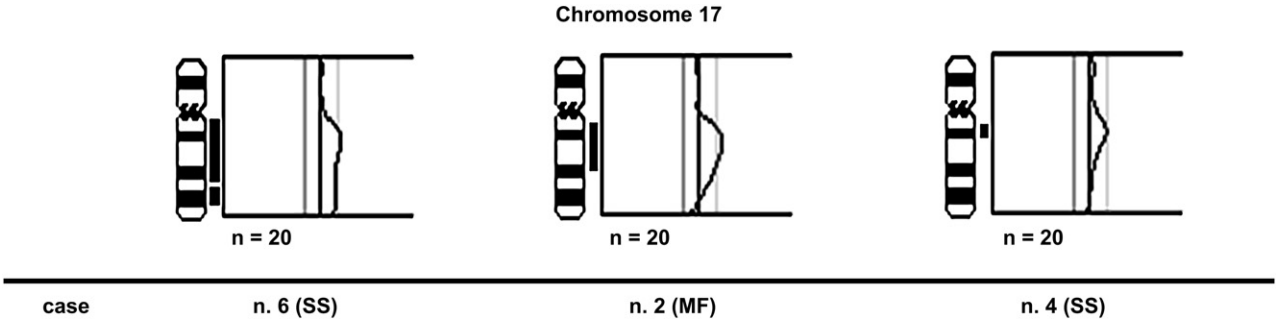

Fig. 1. Representative samples from comparative genomic hybridization analysis of 10 metaphases identified the minimal common duplicated region on 17q, corresponding to band 17q11.2~q12, in patient 4. Duplication regions are represented by thick bars between the profile and the chromosome diagram. *Abbreviations:* MF, mycosis fungoides; SS, Sézary syndrome.