Acta Derm Venereol 2004; 84: 463–468

Taylor & Francis
healthsciences

CLINICAL REPORT

Lymphomatoid Papulosis Associated with Mycosis Fungoides: Clinicopathological and Molecular Studies of 12 Cases

Fernando GALLARDO[1,2], Carlota COSTA[2,3], Beatriz BELLOSILLO[3], Francesc SOLÉ[3,4], Teresa ESTRACH[2,5], Octavio SERVITJE[2,6], María Pilar GARCÍA-MURET[2,7], Carlos BARRANCO[3], Sergi SERRANO[3] and Ramon M. PUJOL[1,2]

[1]*Department of Dermatology and Pathology, Hospital del Mar, IMAS, Barcelona,* [2]*Catalonian Cutaneous Lymphoma Network, Barcelona,* [3]*Laboratory of Cytogenetics and Molecular Biology, Department of Pathology, Hospital del Mar, IMAS, Barcelona,* [4]*Haematologic Cytology School, Soledad Woessner-IMAS, Barcelona,* [5]*Departments of Dermatology, Hospital Clínic, IDIBAPS, Universitat de Barcelona,* [6]*Ciutat Sanitària i Universitària de Bellvitge, Barcelona and Hospital Santa Creu i Sant Pau, Barcelona, Spain*

The association of mycosis fungoides and a primary cutaneous CD30+ lymphoproliferative disorder has been reported and probably represents different clinical aspects of a unique T-cell monoclonal expansion. In this study, 12 patients (6 men and 6 women) presented with lymphomatoid papulosis and mycosis fungoides. A TCRγ gene rearrangement study was performed by an automated high-resolution PCR fragment analysis method on skin biopsy specimens taken from the different clinical lesions in each patient. An indolent clinical course was observed in the majority of patients. T-cell clonality was identified in 7 of 12 lymphomatoid papulosis lesions (58%) and in 6 skin biopsies of plaque stage mycosis fungoides (50%). In each individual case, where T-cell clonality was detected, both mycosis fungoides and lymphomatoid papulosis specimens exhibited an identical peak pattern by automated high-resolution PCR fragment analysis, confirming a common clonal origin. Only one case showed a clonal TCRγ rearrangement from the lymphomatoid papulosis lesion, which could not be demonstrated in the mycosis fungoides specimen. The demonstration of an identical clone seems to confirm that both disorders are different clinical manifestations of a unique T-cell monoclonal proliferation. Our results also seem to confirm that the association of mycosis fungoides with a primary cutaneous CD30+ lymphoproliferative disorder usually carries a favourable prognosis. *Key words: mycosis fungoides; lymphomatoid papulosis; T-cell clonality; PCR; Genescan.*

(Accepted April 23, 2004.)

Acta Derm Venereol 2004; 84: 463–468.

Fernando Gallardo, Department of Dermatology, Hospital del Mar, IMAS, Passeig Marítim 25-29, 08003-Barcelona, Spain. E-mail: FGallardo@imas.imim.es

The simultaneous observation of a CD30+ cutaneous lymphoproliferative disorder (lymphomatoid papulosis [LyP]/primary cutaneous large T-cell CD30+ lymphoma [CD30+ large CTCL]) and other malignant lymphomas (mycosis fungoides [MF] or Hodgkin's disease) is uncommon (1–3). When present, both processes could develop simultaneously or precede one another by months to years. Several authors have pointed out that MF cases associated with a CD30+ cutaneous lymphoproliferative disorder seem to have an indolent clinical evolution and a more favourable prognosis (4, 5).

The clonal relationship between these lymphoproliferative disorders has been addressed in only a few cases to date, possibly for technical reasons, such as a sparse lymphoid infiltrate in skin specimens or a limited technical sensitivity to detect clonal TCR-γ gene rearrangements (3).

In the present study, we reviewed the clinical, histopathological and immunophenotypic features in a series of patients presenting with both MF and LyP from the Catalonian Cutaneous Lymphoma Network (Barcelona, Spain). T-cell clonality was evaluated by PCR and GeneScan analysis (PCR-GSA). The clonal relationship between MF and LyP lesions in each individual patient was investigated.

MATERIALS AND METHODS

Patients

Twelve patients with a proven diagnosis of MF associated with LyP were included in the study.

The diagnosis of each sample specimen was established on the basis of clinical data, routine histopathological examination and immunophenotypic expression. The features were evaluated according to the standard criteria for the diagnosis of primary cutaneous T-cell lymphoma of the WHO and EORTC classifications (6, 7). All biopsy samples were obtained simultaneously for histopathological and molecular diagnostic purposes.

An individualized clinical protocol was applied to all cases presenting the association of MF and LyP. The clinical charts were reviewed by doctors from the different hospitals in Catalonia (Catalonian Cutaneous Lymphoma Thematic Network).

Methods

Histopathological and immunophenotypic studies. The diagnosis of LyP and MF was established on the basis of routine haematoxylin and eosin (H&E) examination. Immunophenotypic

 ISSN 0001-5555
DOI: 10.1080/00015550410016949

analysis was performed by applying a panel of cell surface lymphoid markers. The studies were performed in all cases using formalin-fixed paraffin-embedded tissue sections with en-Vision technique in an automated immunostainer, using the antibodies CD3, CD8, CD20, CD30 (DAKO, Glostrup, Denmark), CD4 and CD56 (Novocastra, Newcastle, UK). Immunohistochemical features were evaluated in both MF and LyP lesions with special attention being paid to the CD30 antigen.

Genotypic analysis. The DNA was extracted from paraffin-embedded biopsies using a QIAamp Tissue Kit (QIAGEN GmbH, Hilden, Germany). Thus, 200 ng of genomic DNA were amplified by PCR as described previously by Dippel et al. (8), but with the following modification: only one amplification was performed using the oligonucleotide primers $V\gamma 2_{1-9}$ (5′ ACG GCG TCT TC(AT) GTA CTA TGA C 3′) labelled with FAM, JGT_3 (5′ AGT TAC TAT GAG C(CT) AGT CCC 3′) and $JGT_{1/2}$ (5′ AAG TGT TGT TCC ACT GCC AAA 3′).

Fluorescent fragments analysis (GeneScan analysis – GSA). One μl of the PCR product was mixed with 9 μl of deionized formamide (Applied Biosystems, Foster City, CA, USA) and 0.5 μl of molecular weight standard (Genescan 400-ROX, Applied Biosystems). The samples were analysed by an automated fragment ABI 3100 (Genescan system).

The diagnosis of T-cell clonality was established when only one or two peaks of approximately 200 bp were observed in all PCRs. Polyclonal cases showed multiple peaks. TCRγ PCR-GSA analysis was performed in triplicate for each skin biopsy to avoid a false-positive interpretation of monoclonality (pseudomonoclonality).

RESULTS

Clinical data

The clinical features, the chronological sequence of both disorders, the different treatments and the clinical outcome are summarized in Table I.

Twelve patients (mean age 49 years) were included in the study. The cutaneous lesions were considered clinically diagnostic of plaque stage MF in eight patients, whereas in four patients the clinical diagnosis was MF patch stage (Fig. 1A). Recurrent, self-healing crops of papules or nodules consistent with LyP were observed in all the patients (Fig. 1B). One patient (case 2) had been diagnosed and treated for Hodgkin's disease 18 years previously. Another patient (case 6) had developed a CD30+ large CTCL. The onset of both disorders was simultaneous in four patients, with an overall follow-up ranging from 4 to 40 years (mean duration of 10 years). In eight cases, MF lesions preceded the development of LyP by a period ranging from 2 to 35 years (mean 7 years).

PUVA was the first-line treatment for MF lesions in nine cases. Two patients with MF patch stage controlled the disease with topical corticosteroids. In one patient (case 12), electron beam radiotherapy was chosen for treatment of widespread cutaneous lesions. An improvement of the disease was achieved in seven cases (two patients with complete remission). Interferon-α 2a was prescribed in two patients presenting cutaneous relapses of MF after PUVA treatment. In case 12, who presented an aggressive long-standing MF with multiple tumoral lesions and extracutaneous involvement, a chemotherapeutic regime was necessary. In the majority of cases, LyP lesions were not treated. In four patients low-dose oral methotrexate was prescribed because of the number and the evolution of lesions. At present, most patients still have active lesions of MF (patch/plaque stage) and/or LyP relapses.

Histopathological and inmmunohistochemical features

Several skin biopsy specimens (from 2 to 10) were evaluated in each patient. In four cases, histopathological examination of MF patches disclosed a discrete

Table I. *Clinical characteristics and results of the 12 cases with primary cutaneous T-cell lymphoproliferative (CTCL) disorders mycosis fungoides (MF)/lymphomatoid papulosis (LyP)*

Case no.	Age/sex	CTCL	Onset*	Follow-up (years)	Current status	Treatment	TCR-γ-PCR-GSA (MF)	TCR-γ-PCR-GSA (LyP)
1	55/M	MF/LyP	S	10	Alive	PUVA, MTX	Non-clonal	Non-clonal
2	40/M	MF/LyP/HD	HD (18 y) S	5	Alive	PUVA, IFN, retinoids, BCNU	Clonal	Clonal
3	70/M	MF/LyP	S (7 y)	7	Alive	PUVA, MTX	Clonal	Clonal
4	69/M	MF/LyP	MF (6 y)	10	Alive	PUVA, MTX	Clonal	Clonal
5	52/M	MF(p)/LyP	S	8	Alive	PUVA	Non-clonal	Non-clonal
6	72/F	MF/LyP	MF (2 y)	4	Alive	PUVA, MTX	Clonal	Clonal
7	46/F	MF/LyP	MF (5 y)	15	Alive	PUVA, BCNU	Clonal	Clonal
8	40/F	MF(p)/LyP	MF (3 y)	5	Alive/CR	Topical steroids	Non-clonal	Non-clonal
9	40/F	MF(p)/LyP	MF (7 y)	12	Alive	Topical steroids	Clonal	Clonal
10	40/F	MF(p)/LyP	MF (19 y)	21	Alive	PUVA	Non-clonal	Non-clonal
11	41/F	MF/LyP	MF (10 y)	15	Alive/CR	PUVA	Non-clonal	Non-clonal
12	73/M	MF/LyP	MF (35 y)	40	Dead Lymphoma	RT, IFN, ChT (COP) (VP-16)	Pseudoclonal (non-clonal)	Clonal

HD, Hodgkin's disease; MF(p), MF patch stage; S, simultaneous; Alive, active lesions of MF/LyP; CR, complete remission (no lesions); RT, radiotherapy; ChT, chemotherapy; IFN, interferon; MTX, methotrexate; BCNU, carmustine.
*Initial presentation and interval between both disorders.

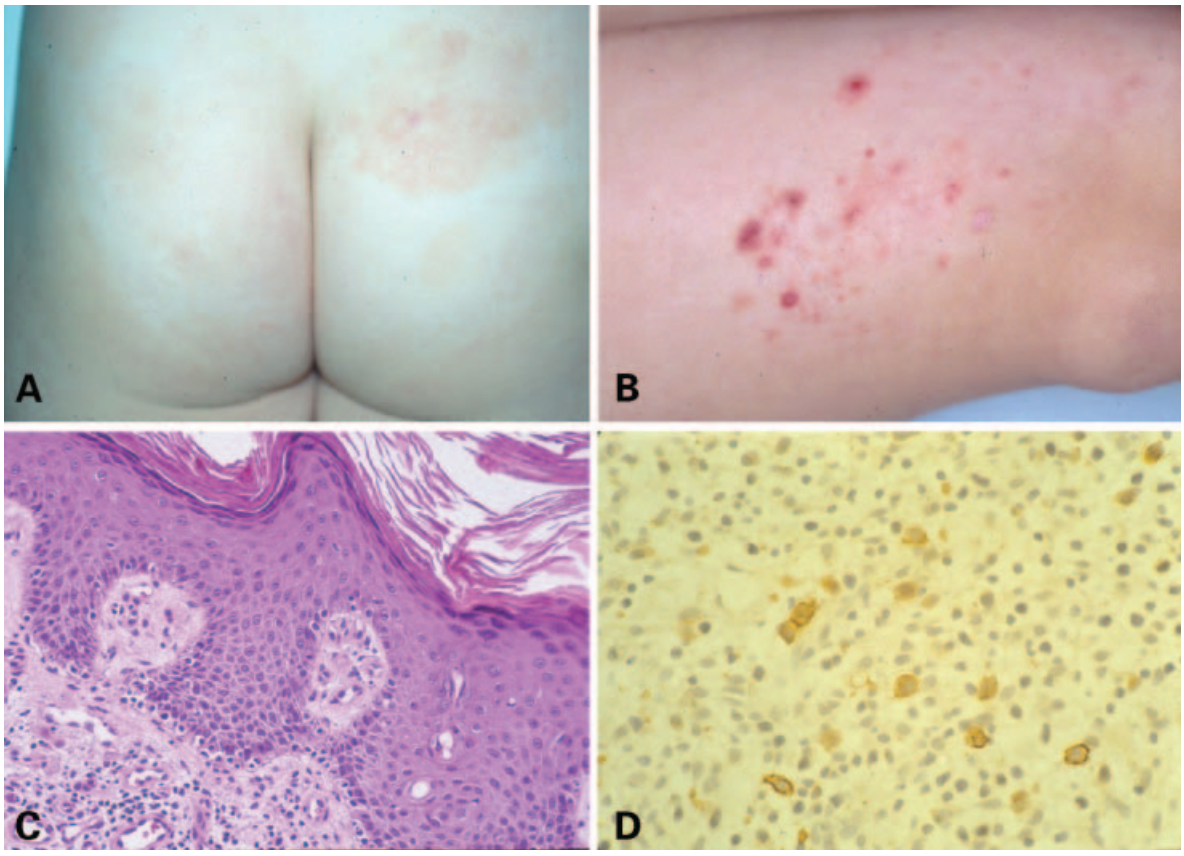

Fig. 1. (A) Clinical features of mycosis fungoides patch lesions. (B) Lymphomatoid papulosis. Recurrent necrotic papules. (C) Mycosis fungoides (patch stage). Single cell epidermotropism by atypical lymphocytes with convoluted nuclei (H&E ×200). (D) Lymphomatoid papulosis. Large atypical cells expressing CD30 antigen (CD30 ×400).

band-like inflammatory infiltrate. This involved the papillary dermis with single cell epidermotropism showing a histopathological picture consistent with patch stage MF (Fig. 1C). In these cases, single skin biopsy specimens may have proved non-diagnostic and therefore repeated observations and the practice of repeated biopsies were necessary to establish a definitive diagnosis. In eight MF biopsies, a classic histopathological picture of plaque stage MF was observed. Neoplastic cells expressed a T-helper cell phenotype CD3+, CD4+, CD8−, CD20−, CD30− and CD56−.

All LyP lesions exhibited a characteristic dense wedge-shaped mixed inflammatory infiltrate with isolated and clustered large atypical cells (histological type A LyP). Atypical large cells expressed perinuclear CD30 antigen within a background of T-helper (CD4+) lymphocytes (Fig. 1D).

TCRγ gene rearrangement and GeneScan analysis

In the PCR-GSA method used, 6 of 12 MF samples and 7 of 12 LyP samples showed a monoclonal expansion. A concordance between MF/LyP samples from the same patient was achieved in 11 of 12 cases and the amplification fragments showed identical TCRγ rearrangements from MF and LyP lesions in 6 patients (cases 2, 3, 4, 6, 7 and 9) (Fig. 2). In the remaining 5 patients, we could not demonstrate clonality in either MF or LyP samples. In one case (case 12), a clonal peak was detected in the LyP lesion, whereas a pseudoclonal pattern was detected in the MF lesion (different peaks were observed after repeated PCR-GSA).

DISCUSSION

It is now generally accepted that primary CD30+ cutaneous lymphoproliferative disorders comprise a clinical and morphological spectrum, in which a clear distinction between LyP and lymphoma cannot always be established (9–22). In some patients, LyP precedes, is associated with, or is followed by primary cutaneous CD30+ lymphoma. Primary cutaneous CD30+ disorders are usually characterized by an indolent clinical course and a good prognosis (12–15).

The association of MF and a cutaneous CD30+ lymphoproliferative disorder in the same patient seems to be an uncommon, but not exceedingly rare phenomenon (16, 17). In patients with LyP, development of MF or other malignant lymphoproliferative disorders has been reported in between 5 and 15% of cases (5, 18–20). In some instances, LyP and MF seem

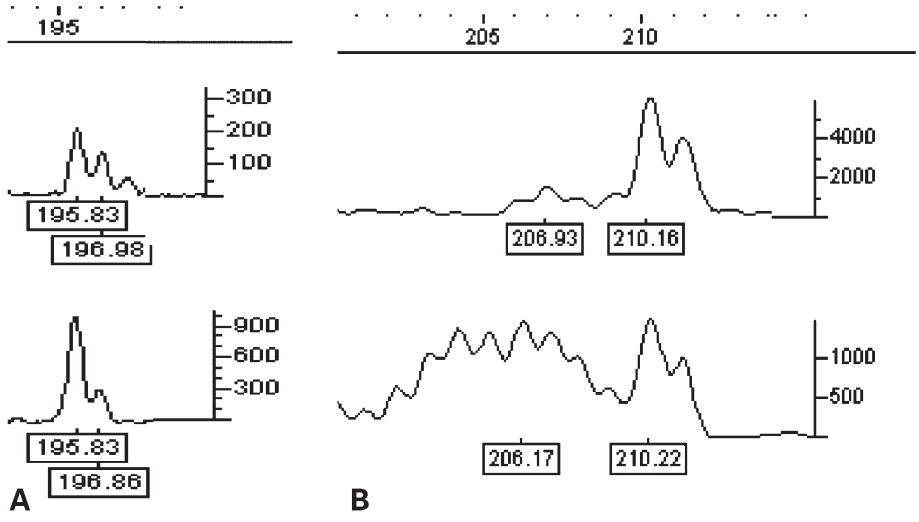

Fig. 2. TCRγ PCR-GSA showing the same amplification DNA fragment in both mycosis fungoides (upper panel) and lymphomatoid papulosis (lower panel) biopsies in patient 4 (A) and patient 6 (B), respectively.

to co-exist as clinically independent disorders, probably as manifestations of a common clonal origin (21).

The onset of both MF and LyP may be simultaneous or precede one another by months or years. After reviewing the clinical features and the evolution of a series of 15 patients presenting with LyP in association with MF, Basarab et al. (22) suggested that this group of patients seems to have a more favourable prognosis. More recently, Zackheim et al. (23) reported a series of 21 patients with similar results. The majority of MF lesions observed in our series also corresponded to early lesions (patches and plaques). In some instances, the definite diagnosis of MF was established after repeated biopsies and the evaluation of several skin biopsies.

In our series, all MF cases corresponded to stages IA (33%) or IB (66%). An indolent clinical course was observed and no evolution to more advanced stages after a prolonged follow-up period was noted with the exception of one patient. This patient developed tumours and died of advanced CTCL.

An association of CD30+ large CTCL and MF has also been reported. Cases of MF which developed CD30+ large CTCL should be distinguished from MF showing large cell transformation as they usually have an aggressive clinical course. This differentiation may be extremely difficult or even impossible based exclusively on the histological and immunophenotypical features (4, 24–27).

Since the original description of this association, a pathogenetic relationship between both disorders has been postulated (28). The demonstration of a common clonal origin could theoretically be demonstrated by means of genotypic analysis. Nevertheless, conventional PCR-based techniques detect T-cell monoclonality in only 50% of LyP lesions, and this percentage is even lower in early MF lesions. The presence of a sparse lymphoid infiltrate often admixed with a non-neoplastic reactive lymphoid population may explain these results. Other possible reasons might be the absence of rearrangement of the γ chain locus in a particular case, the lack of coverage of all possible V-J rearrangements of the TCRγ locus (i.e. rearrangements of the Vγ10–Vγ12 segments were not covered by our selected set of primers) and specific limitations of the different technical approaches (29, 30).

Recently, in order to improve the sensitivity of this analysis, several technical modifications have been introduced in the studies of T-cell clonality. PCR-GSA is a new method, which determines dominant T-cell clones. It seems to be sensitive, accurate, specific and easier to interpret than standard electrophoresis gel techniques (8). GSA is a simple quick test with a low overall cost. This enables an accurate determination of the size of PCR products and distinguishes between polyclonal and monoclonal DNA patterns. In our experience, this technique can detect a T-cell clone at tumour densities as low as 2%, whereas other authors have detected densities from 0.5 to 1% (8). The method seems suitable for analysing skin lesions, where the lymphoid infiltrate is usually sparse. In addition, it allows the demonstration of the identity of two different clonal populations showing an identical peak size without performing a direct sequencing of the PCR products (31). Therefore, it is a valuable tool, which demonstrates a common clonal origin between different clinical entities. However, taking into account that a single dominant peak has been observed after PCR-GSA analysis in some cases of benign inflammatory cutaneous disorders, repeated determinations to confirm a clonal dominance are necessary. Differences in the size of the dominant PCR products after repeated determinations may be interpreted as false positive results (pseudomonoclonality). Using this method, T-cell clonality could be demonstrated in 58% and 50% of patients with LyP and early MF lesions, respectively, in our series. Clonally rearranged TCR genes have been

Table II. *Reported patients with clonality-related mycosis fungoides (MF)/lymphomatoid papulosis (LyP)*

Author	Disease	T-cell RG	Method
Davis 1992 [39]	HD, LyP, CTCL	1/1	PCR TCRα
Wood 1995 [25]	LyP, CD30+ CTCL, MF	3/3	PCR/DGGE TCRγ
Chott 1996 [37]	LyP, CD30+ CTCL, MF	4/11	PCR TCRβ/γ
Basarab 1998 [22]	MF/LyP	3/15	SBA/PCR-SSCP
Assaf 2003 [31]	T-PLL, MF, LyP, CD30+ CTCL	1/1	PCR TCRβ/γ
Zackheim 2003 [23]	LyP, MF	7/21	PCR heteroduplex

T-cell RG, T-cell rearranged monoclonal population (concordant cases/analysed cases); HD, Hodgkin's disease; SBA, southern blot analysis; DGGE, denaturing gradient gel electrophoresis; PCR-SSCP, polymerase chain reaction-single strand conformational polymorphism; T-PLL, T-cell prolymphocytic leukaemia.

detected in approximately 60% of LyP lesions, depending on the series and techniques employed. Identical rearrangements have been demonstrated from both LyP and associated cutaneous lymphoma lesions (32, 33).

Recently, Steinhoff et al. (34), by using laser beam microdissection and single cell PCR-TCRγ with GSA analysis, have demonstrated the clonal nature of atypical CD30+ cells in LyP. In 14 skin biopsies of patients suffering from LyP, CD30+ cells showed a clonal TCRγ rearrangement. Moreover, the CD30- cells admixed in the LyP infiltrate, when individually analysed, displayed a polyclonal TCRγ rearrangement (34). Conversely, Gellrich et al. (35) failed to detect a monoclonal T-cell population in CD30+ single cells obtained from clonal cases of LyP. The authors speculated that CD30+ large T-lymphocytes do not represent a uniform tumour cell population in CD30+ lymphoproliferative disorders encompassing neoplastic cells, bystander T-cells and occasionally additional clones (35).

However, several genetic studies have pointed out the presence of a unique clonal expansion in cases of MF associated with a primary cutaneous CD30+ lymphoproliferative disorder. Basarab et al. (22) demonstrated that MF and LyP lesions had an identical clone in 3 of 15 patients by Southern blot analysis and PCR single-strand conformational polymorphisms (PCR-SSCP). Similar findings have been reported by Wood et al. (36) in two patients with MF and LyP, employing PCR-denaturing gradient gel electrophoresis (PCR-DGGE) and sequencing of the TCRγ PCR products. In two further cases with co-existing MF and LyP, Chott et al. (37) also reported identical T-cell clones by PCR-TCRγ and β-chain gene rearrangement from both types of lesions. Assaf et al. (31), employing the PCR-GSA method, demonstrated a common clonal origin in one unusual case of indolent T-cell prolymphocytic leukaemia, which subsequently developed MF, LyP and CD30+ anaplastic lymphoma. This was also confirmed by the cytogenetic alterations detected by *in situ* hybridization in different clones. More recently, Zackheim et al. (23) studied seven patients and found an identical clone in lesions of both LyP and MF by performing PCR heteroduplex analysis (Table II).

The coexistence or subsequent development of different malignant lymphomas (i.e. Hodgkin's disease, T-cell immunoblastic lymphoma) in the same patient harbouring identical clones has been reported in some instances (3, 11, 37, 38).

In conclusion, our results show the simplicity of automated fluorescent fragment analysis by GSA in the study of T-cell monoclonal populations. We also illustrate the utility of this technique in demonstration of an identical T-cell clonal population from different and coexistent cutaneous lymphoproliferative disorders. Moreover, this study supports, as has been previously suggested, that MF and LyP may represent, in some instances, different clinical manifestations of an identical T-cell lymphoproliferative clonal expansion.

ACKNOWLEDGEMENTS

The authors want to thank Mari Carmen Vela and Anna Pérez Lezaun for their excellent technical assistance. The samples were obtained from the Xarxa Temàtica de Limfomas Cutànis de la Generalitat de Catalunya 2002/XT/00020. This study was partially supported by the grants FIS 01/1424, FIS 02/0002 and G03/179 from the Spanish "Ministerio de Sanidad y Consumo".

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