Atypical lymphoproliferation progressing into B-cell lymphoma in rheumatoid arthritis treated with different biological agents: clinical course and molecular characterization

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A patient with rheumatoid arthritis (RA) developed an atypical lymphoproliferative disorder (LPD) after methotrexate and cyclosporine A, which regressed after suspension of both drugs. After subsequent treatment with rituximab, the LPD was still undetectable. Anti-tumor necrosis factor α therapy was used when the arthritis relapsed, but an aggressive B-cell non Hodgkin's lymphoma developed. Molecular analyses showed an oligoclonal B-cell expansion at the LPD step. A minor clone with significant sequence homology to B-cell lymphomas arising in Sjögren's syndrome and mixed cryoglobulinemia syndrome, given rise to the non-Hodgkin's lymphoma. Treatment of rheumatoid arthritis associated with lymphoproliferation represents a clinical challenge, and common pathogenetic pathways to lymphoma may occur in different autoimmune diseases.

Key words: rheumatoid arthritis, lymphoma, rituximab, tumor necrosis factor.

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Rheumatoid arthritis (RA) is a well-recognized condition predisposing to malignant lymphoma, usually a B-cell non-Hodgkin's lymphoma (NHL).[1-5] B cells play a crucial role at least in some subsets of RA patients,[6-8] and both chronic inflammation and ongoing antigenic B-cell stimulation related to the disease may favor the stochastic emergence of a neoplastic B-cell clone.[9,10] The molecular evidence of chronic antigenic B-cell stimulation in RA and the increased incidence of NHL in patients with RA of longer duration support this notion.[1-5] Chronic immunosuppression due to RA therapy, leading to loss of immunosurveillance, might also play a role.[11] Treatment options that may be effective on RA without favoring B-cell expansion should be better defined.[6,7] We report the clinical course of a patient with RA who developed a non-malignant atypical lymphoproliferative disorder (LPD)[12] which then progressed into an aggressive B-cell NHL, and discuss the case with reference to the different immunosuppressive and biological treatments employed. In addition, the B-cell disorder was characterized by molecular studies, which supported our data interpretation and shed some light on possible similarities between lymphoproliferation in RA, Sjögren's syndrome and mixed cryoglobulinemia syndrome.[13]

Design and Methods

Clinical data

A 77-year old woman was admitted to our Clinic in October 1999 with fever, sweating, axillary lymphadenopathy and splenomegaly. She had been affected by rheumatoid factor (RF)-positive RA since 1949. The patient had been treated with steroids for many years, then with methotrexate. In June 1999 cyclosporine A (2.5 mg/kg/day) was combined with methotrexate (15 mg/week). The patient did not have Sjögren's syndrome or mixed cryoglobulinemia syndrome and was negative for hepatitis B and C virus (HCV) infection. In October 1999 her lactate dehydrogenase (LDH) increased and a computed tomography scan (CT) demonstrated multiple enlarged lymph nodes in the mediastinum and retroperitoneum, splenomegaly and hepatomegaly. Nodal biopsy showed an atypical LPD (Figure 1). Variable, diversity and joining (V-D-J) region rearrangements of tissue immunoglobulin heavy chain amplified by polymerase chain reaction (PCR)[9] showed an oligoclonal pattern of B-cell expansion, while the Epstein Barr virus was not detected by PCR or *in situ* hybridization. The bone marrow was uninvolved. Methotrexate was stopped in March 2000 without improvement. Then, cyclosporine A was stopped and methotrexate was reintroduced since the woman's synovitis had worsened; again there were no improvements in LPD manifestations. In January 2001 a second nodal biopsy showed unchanged histopathological features. Methotrexate was then interrupted and the LPD completely regressed by March 2001 as shown by physical examination and by negative chest X-rays and ultrasound of the abdomen. However, the patient's arthritis was still very active. Chloroquine and sulphasalazine were ineffective. In August 2001 repeated CT demonstrated normally sized spleen and liver, and lymph nodes sized less than 1 cm in the mediastinum and retroperitoneum. The patient then underwent four intravenous weekly infusions of rituximab (375 mg/m^2): RA responded,[6] RF became negative, and features of LPD were absent. In January 2002 the patient's RA relapsed, but a second course of rituximab could not be repeated because of its high costs. Leflunomide was not tolerated. Etanercept 25 mg twice weekly was started in April 2003. A total-body CT repeated at that time was unchanged compared to that performed in August 2001. In November 2003

the patient developed fever, fatigue and itching, and increased LDH, while her RA was well controlled. A total-body CT showed several enlarged thoracic and abdominal lymph nodes and an abdominal nodal mass of 12×8 cm; the needle biopsy of this mass demonstrated a diffuse large B-cell NHL.[14] The bone marrow was uninvolved.

Molecular studies

DNA from the LPD specimens taken in June 1999 (LPD99) and January 2001 (LPD01) were amplified by PCR using the seminested heavy chain V-D-J-third framework region (FR3) protocol,[8] revealing an oligoclonal (LPD99) and a polyclonal (LPD01) pattern of B-cell expansion, while the neoplastic abdominal mass (NHL04) showed a fully monoclonal pattern. The oligoclonal bands of the LPD99 FR3-PCR and the monoclonal band of the NHL04 FR3-PCR products were purified and cloned in a bacterial vector (TOPO-TA cloning kit, Invitrogen). Sixteen colonies, chosen at random, for the LPD99 and seven colonies for the NHL04 FR3-PCR products were sequenced (Table 1). Strikingly, the seven sequences of the neoplastic B-cell clone (NHL04-1) were nearly identical to those of a minor clone of the LPD99 lesion (LPD99-6 clone) (Table 1 and Figure 2). To identify the *VH* genes of the neoplastic clone, multiple PCR were prepared, each containing a forward primer specific for the FR1 region of each of the VH families (VH1 to VH6) and a reverse primer consisting of a mixture of JH primers.[15] The VH1 family was used by the neoplastic B-cell clone. The whole PCR product was cloned and sequenced, and then different clone-specific PCR approaches (with primers designed on the NHL04 sequence; *data not shown*) confirmed that the clone giving rise to the lymphoma was already present in the preneoplastic LPD99 lymph node biopsy (LPD99-6 clone) (Figure 2), while it was undetectable in the LPD01 polyclonal specimen, as well as in both peripheral blood and bone marrow mononuclear cells obtained at the time of lymphoma diagnosis. The NHL04 B-cell clone sequences were compared, using the V-QUEST program, with the germline genes in the IMGT directory. The best fitting germline sequence was IGHV1-69*01. Similarly, the rearranged light chain gene was amplified,[13] cloned and sequenced revealing its best fit with the IGKV3-20*01 germline sequence. A multi-

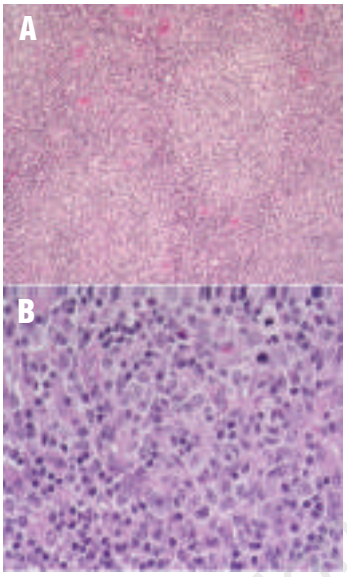

Figure 1. Nodal atypical lymphoproliferative disorder of the reported case. **A.** Low power view of the LPD99 lymph node biopsy, showing a follicle and a markedly expanded paracortical area, rich in high endothelial venules (H&E, 10×). **B.** High power view of the paracortical area of the same biopsy: a few small lymphocytes with irregular nuclei are evident among an expanded lymphoid proliferation of large cells with B morphology (centrocytic cells, centroblasts, occasional immunoblasts). Many mitoses are evident (H&E, 40×).

Table 1. Nucleotide and deduced amino acid sequences of the cloned FR3-PCR products obtained by the amplification of the DNA from the nodal specimens LPD99 and NHL04. The putative specificity of each CDR3-IgH sequence was found by submitting the deduced amino acid sequence in the Translate BLAST search protein program (*http://www.ncbi.nlm.nih.gov/blast/*) considering the first five best fitting alignments characterized by higher values of homology (>80- 90%).

Subclone name	*N° of identical colonies*	*Sequence*	*Translation*	*Putative activity*
LPD99-1	3	5'-ACACGGCTGTATTACTGTGCACGGCAAA GTAGTGGTTATTACTACTCGTTATCAAGGGTACTGGTTCGACCC CTGGGGCCAAGGCACCCTGGTCAC-3'	TALYYCARQ SSGYYYSLSR VLVRPLGPR HPGH	Autoimmune repertoire (MG, SLE)
LPD99-2	2	5'-ACACGGCTCTGTATTACTGTGGGAGAAGT TATGGTTCGGGGAGTTATGGAGTTGACTACTGGGCCAA GGCACCCTGGTCA-3'	TRLCITVGEV MVRGVMEL TTGAKAPWS	Human Ig unspecified
LPD99-3	3	5'- ACACGGCTCTGTATTACTGTGCGAGGCTTC TTTCGGAGGCTGAGGGATACTTTGACTACTG GGGCCAAGGCACCCTGGTCAC-3'	TALYYCARL LSEAEGYFD YGQGTLV	Ig produced by synovial B cells
LPD99-4	6	5'-ACACGGCTCTGTATTACTGTGCGAGAGTG GGGTGGATAGAAGCAGCGGGGGGCGTTAACT ACTGGGGCCAAGGCACCCTGGTCAC-3'	TALYYCARV GWIEAAGGV NYWGQGTLV	Human unspecified
LPD99-5	1	5'- ACACGGCTCTGTATTACTGTGCGAGAGATC TTTTCTGTTTGAGTATAGCAGTGGCTGGTCCGA CTACTGGGGCCAAGGCACCCTGGTCAC -3'	TALYYCARD LFCLSIAVA#S	Autoimmune repertoire (aCL)
LPD99-6	1	5'-ACACGGCTCATGTATTACTGTGCGAGAGAG GGGAGGCAGATGGCTTCAAACCCCTTTGACT ACTGGGGCCAAGGCACCCTGGTCAC-3'	TAMLYYCAR EGRQMASNP FDYWGQGTLV	RF*
NHL04	7	5'-ACACGGCTACTGTATTACTGTGCGAGAGA AGGGAGGCAGATGGCTACAAACCCGTTTGACT ACTGGGGCCAAGGCACCCTGGTCAC-3'	TAMLYYCAR EGRQMATNP FDYWGQGTLV	RF°

*MG: myasthenia gravis; SLE, systemic lupus erythematosus; aCL, anticardiolipin antibody. *Detailed analysis revealed that the clone NHL04 (seven identical sequences) was already present at the stage of the LPD99 (see text and Figure 1). The nucleotide alignment between the FR3-JH regions of the LPD99-6 and NHL04 clone revealed two silent and one replacement mutation in the latter. The replacement mutation was Ser in LPD99-6 to Thr in NHL04. °Submission of the sequences to the Translate BLAST search protein program revealed a high homology with the following RF: 1) gi|225800|prf||1313976A: Rheumatoid factor BOR [Score: 86.3 bits (196), Expect: 7e-17; Identities: 25/27 (92%), Positives: 26/27 (96%)]; 2) gi|510402|emb|CAA84416.1|: IgM, variable region, rheumatoid factor, autoantibody- Homo sapiens; [Score: 77.0 bits (174), Expect: 5e-14 Identities: 22/26 (84%), Positives: 25/26 (96%)].*

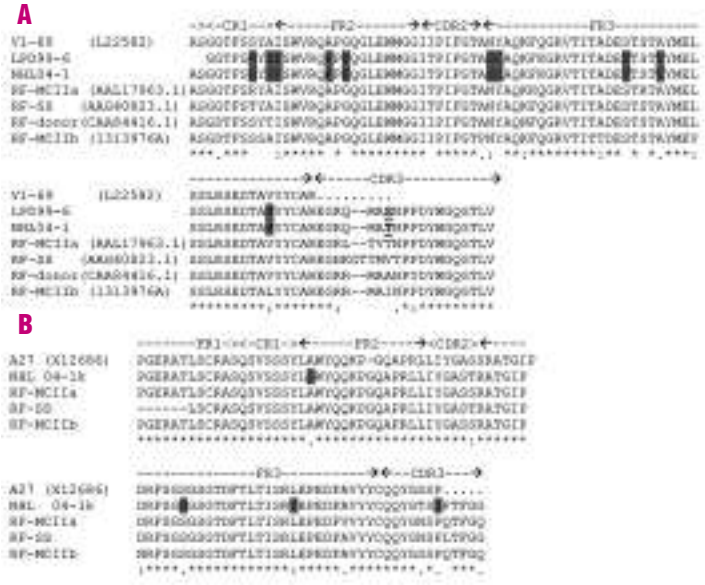

Figure 2. The deduced amino acid sequences of the heavy (panel A) and light (panel B) chain variable regions of NHL04-1 and LPD99-6 samples are reported (only the heavy chain was analyzed for LPD99-6), in conjunction with the most similar database sequences. All the sequences employed the VH1-69 and VK3.20 genes, corresponding to the germline V1-69 and A27 amino acid sequences shown. The number of the corresponding NCBI genbank sequence is indicated in parentheses. The light gene sequences of RF-mixed cryoglobulinemia type II (MCII) (a and b clones) and RF-Sjögren's syndrome (SS) belong to the corresponding clone in panel A. All these database sequences encoded RF. The VK sequence and antibody specificity of the sequence *RF-donor* is not known. Identical amino acids are reported by dashes, amino acid substitutions with conserved physico-chemical properties are reported by ":", semi-conserved substitutions are reported by ".", while a blank space indicates completely different amino acids. Changes in the LPD99-6 and NHL04-1 sequences with respect to germline are evidenced in gray. Alignment of the NHL04-1 and LPD99-6 sequences shows that ten identical amino acid substitutions are shared, consistent with the common origin from the same progenitor clone; one additional amino acid change in the CDR3 region (one substitution of Ser to Thr, reported in bold and underlined; see also Table 1) is present in the NHL04-1 clone.

nomial distribution model[16] assessed the statistical significance of an excess or scarcity of replacement mutations in complementarity determining regions and framework regions (*www.stat.stanford.edu/immunoglobulin*). The replacement/silent mutation ratio showed a lower than expected value only in the framework regions (p=0.04) of the *IGH* sequence, consistent with the preservation of immunoglobulin (Ig) functional structure, while the ratios of the complementarity determining regions of both VH and VK and the framework regions of VK were not significantly different from the expected value. Very limited intraclonal heterogeneity was found among the different subclones (six subclones for IgH, with 5/6 identical sequences named NHL04-1; and 12 subclones for IgK, with 6/12 identical sequences named NHL04-1k), as expected in aggressive NHL (*data not shown*). Submission of the NHL04 clone heavy and light chain gene sequences to IgBLAST showed a significant similarity to the Ig gene sequence of LPD occurring in other autoimmune diseases predisposing to lymphoma, i.e., Sjögren's syndrome and mixed cryoglobinemia syndrome (Figure 2), in which RF-binding activity of the proliferating clone has also been demonstrated by functional studies.[17,18] To investigate the reactivity of the tumor immunoglobulin we employed *in vitro* generated antibodies identical to those produced by lymphoma cells. The Ig VH and VK rearrangements of lymphoma were amplified, cloned and expressed as single chain fragment variable (scFv) antibody. For this purpose the Ig-VH and VK genes (dominant sequences) of case NHL04 were cloned into the pIVEX 2.4c vector (Roche) that contains the coding sequence for the $(G_4S)_3$ peptide linker for joining the heavy and light chains and a His-tag. For complete *in vitro* expression of scFv, the rapid translation system (RTS 100 *Escherichia coli* HY; Roche), which constitutively expresses the reporter gene from a T7 promoter, was used. The gene product was purified by affinity, then identified and quantified by autoradiography following SDS–PAGE. Using an ELISA assay, no RF reactivity was found for scFv (*data not shown*).

Results and Discussion

In this report we highlight the possible different safety profiles of various biological treatments in a patient with RA and an associated B-cell non-malignant LPD. A strict genetic similarity between RA-related lymphoma and lymphomas related to Sjögren's syndrome and mixed cryoglobulinemia syndrome is reported for the first time, suggesting a possible common pathogenetic pathway. Risk factors for NHL development in RA include a higher inflammatory activity, functional class and advancing age,[4] consistent with the concept that chronic inflammation associated with ongoing B-cell proliferation may favor stochastic B-cell oncogenetic events.[9] While effective immunosuppressive treatments for RA may reduce the risk of lymphoproliferation by blocking RA-related chronic inflammation, they may also favor the escape of deregulated B-cell clones. Rituximab therapy proved of value in the patient described here, since it allowed RA control without favoring (and indeed possibly controlling) B-cell lymphoproliferation. Of note, the B-cell clone subsequently evolving into the aggressive B-cell NHL was present in the non-neoplastic, oligoclonal LPD previously diagnosed in 1999. It was not detected in a second, polyclonal LPD lesion biopsied two years later in a different nodal site, consistent with a definitely non-malignant B-cell disorder characterized by the expansion of different B-cell clones in different lesions.[12] Although cyclosporine A rather than methotrexate administration has been related to the emergence of lymphoproliferative disorders in a few RA cases, and has been closely related to post-transplantation LPD, the LPD lesion in our case regressed only after suspension of both the immunosuppressive agents. LPD also remained undetectable after rituximab therapy. The link between anti-tumor necrosis factor-α (TNFα) therapy and the risk of NHL development in RA is still debated.[3-5] Although the literature does not clearly support a role for anti-TNFα therapy in B-cell lymphomagenesis in RA in general, such a role may be hypothesized in single cases. As concerns

our patient, there was a clear temporal relationship between anti-TNFα therapy and lymphoma development. Recently, the protective role of TNFα against NHL evolution was demonstrated in the murine model of TNF$^{-/-}$ B-cell activating factor (BAFF) transgenic mice.[19] Therefore, TNFα blockade may be not advisable when lymphoma is suspected in RA. To our knowledge, no data have been published so far on the antigen specificity of neoplastic B-cell clones in RA. In our case, the clone giving rise to the B-cell NHL was a minor clone detectable in one of the two methachronous nodal biopsies at the pre-neoplastic stage of LPD. The possibility that the homology between the LPD-99 clone and the NHL clone is the result of chance is highly unlikely, since sequence homology was almost complete, and ten common amino acid substitutions were noted (Figure 2). Strikingly, both the heavy and light chain gene sequences of the tumor clone showed a significant similarity with lymphoproliferation occurring in Sjögren's syndrome and mixed cryoglobulinemia syndrome. The RF-binding activity of the proliferating clone has been demonstrated by functional studies,[17,18,20] in the latter diseases. A significant homology with RF sequences was also detected in the case reported here (Table 1), but functional studies with scFv technology did not confirm such antibody specificity. It may be hypothesized that a similar subset of B cells, i.e., employing a restricted pattern of Ig heavy and light chain genes, may also be implicated in RA-related lymphomagenesis, as in the two rheumatic diseases with the highest risk of lymphoma evolution, Sjögren's syndrome and mixed cryoglobulinemia.[8,9] The question of whether RF-positive clones are preferentially involved in RA-related lymphomagenesis remains unanswered. Even in the lack of RF binding activity in the neoplastic clone LPD04, RF activity may have characterized a progenitor clone, with RF specificity then being lost due to somatic mutations (Figure 2). Work is in progress in additional RA lymphoma cases to address this issue. Alternatively, common antigenic epitopes might lead to the antigen-driven proliferation[15,17,20] and preferential expansion of a definite subset of B cells, with some overlap with RF-encoding B-cells. This is a key point for future research. In HCV-related lymphoproliferation, reactivity of the proliferating B-cell clone with HCV antigens has been shown,[20] and our preliminary data also support this possibility (*De Re et al., in press*). Thus, the definition of the antigen specificity of the expanded clones in RA-related lymphomas may be relevant to a better understanding of the etiology of the disease. In conclusion, treatment of RA associated with lymphoproliferation represents a clinical challenge. Our report suggests that rituximab might prove of value in this setting. The possible links between RA-associated lymphomagenesis and lymphoproliferation in Sjögren's syndrome and mixed cryoglobulinemia syndrome[8,13,15] should be thoroughly investigated, and may provide new insights in the etiopathogenesis of RA itself.

LQ: involved in patient identification and follow-up; contributed to to the study design, data interpretation and manuscript writing; VDR: performed molecular analyses; contributed to data interpretation; MF: performed laboratory analyses; contributed to data interpretation and manuscript writing; AM: performed molecular analyses; NF: involved in patient identification and follow-up; DG and LC performed molecular analyses; GF: involved in patient treatment decisions; CAS: performed pathologic studies; contributed to data interpretation; SDV: study co-ordinator; involved in study design, patient selection and treatment, interpretation of data and manuscript writing. *The study was supported by a grant from the Italian Rheumatology Society (Società Italiana di Reumatologia – S.I.R.), by the Italian Ministry of Health (Ministero della Salute) and by the Italian Association for Cancer Research (Associazione Italiana per la Ricerca sul Cancro – A.I.R.C.). We would like to thank Dr. Bronwen M. Lewis for her support in the English language supervision. The authors declare they have no potential conflicts of interest.*

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