Virchows Arch (2005) 447: 778–780
DOI 10.1007/s00428-005-0008-1

LETTER TO THE EDITOR

Jean-Louis Dargent · Laurence Lespagnard · Isabelle Meiers · Christophe Bradstreet · Pierre Heimann · Christiane De Wolf-Peeters

Composite follicular lymphoma and nodular lymphocyte predominance Hodgkin's disease

Received: 17 April 2005 / Accepted: 17 May 2005 / Published online: 28 June 2005

Dear Editor:

Composite lymphoma (CL) is a lymphoid neoplasm in which two (or more) distinct lymphoma subtypes involve the same lymph node or extranodal site [9]. This condition is relatively rare and raises interesting questions about the pathogenesis as well as the relationship that might exist between the various neoplastic components. Recently, we observed the case of a 29-year-old male who developed a distinctive CL consisting of follicular lymphoma (FL) and nodular lymphocyte predominance Hodgkin's disease (NLPHD) within the same lymph node.

The patient was admitted in our hospital because of a slow-growing lymphadenopathy localized in the left inguinal area. This lymphadenopathy spontaneously appeared and progressively increased in size to reach a diameter of almost 4 cm. There was no history of fever or deterioration in the patient's general condition. Clinical examination did not reveal any other abnormality and peripheral blood analysis was within normal limits. Serum investigations for human immunodeficiency virus, hepatitis B and C viruses, Epstein–Barr virus (EBV), cytomegalovirus, and syphilis were negative. In contrast, the patient demonstrated acquired immunity for toxoplasmosis and hepatitis A virus. A surgical excision of the abnormal lymph node was performed for diagnostic purposes.

Microscopically, the nodal architecture was effaced by numerous uniformly sized follicles (Fig. 1). These follicles were closely packed together and lacked mantle zones. They were mostly composed of small centrocytes mixed up with few centroblasts. Tangible body macrophages as well as mitotic figures were almost completely absent. In a small area of the lymph node, we noted several large lymphoid nodules composed of small lymphocytes mixed up with some large atypical cells (Fig. 2). The latter featured the characteristics of "pop corn" cells, indicative of NLPHD (Fig. 3). Both lymphomatous proliferations were relatively well delineated from each other. On immunohistochemical analysis, the lymphoid cells inside the follicles were found to express CD20, CD79a, and CD10. These cells also expressed the bcl-2 and bcl-6 proteins. Small clusters of CD20- and CD10-positive cells were found in the interfollicular areas. "Pop corn" cells showed immunoreactivity with antibodies directed against CD45, CD20, CD79a, and bcl-6 protein. Although some of these cells were weakly CD30-positive, they did not express CD10, CD15, or bcl-2 protein. "Pop corn" cells were found between CD20-, CD79a-, bcl-2 protein-, and CD10-positive centrocytes, CD23-positive follicular dendritic cells, and CD57-positive T lymphocytes. These CD57-positive T lymphocytes often formed rosettes around the "pop corn" cells (Fig. 4). Polymerase chain reaction (PCR) analysis of DNA extracted from the paraffin embedded sections demonstrated a bcl-2 gene rearrangement resulting from a t(14;18) chromosomal translocation in the major breakpoint region. However, no clonal rearrangement of the genes coding for the immunoglobulin (Ig) heavy (IgH) chain or EBV genomic sequences could be evidenced, using the same method of molecular investigation.

Based on these data, a diagnosis of CL consisting of FL and NLPHD was made. Additional investigations revealed the involvement of several lymph nodes located in the left inguinal area, the retroperitoneal and mesenteric regions, and the right axillary area, respectively. No infiltration of

J.-L. Dargent (✉) · L. Lespagnard · I. Meiers
Service d'Anatomie Pathologique, Institut Jules Bordet,
1 rue Héger-Bordet,
1000 Brussels, Belgium
e-mail: jl.dargent@skynet.be
Tel.: +32-2-5413124
Fax: +32-2-5413281

C. Bradstreet
Service de Médecine Interne, C. H. U. Saint-Pierre,
322 rue Haute,
1000 Brussels, Belgium

P. Heimann
Laboratoire de Cytogénétique, Institut Jules Bordet,
1 rue Héger-Bordet,
1000 Brussels, Belgium

C. De Wolf-Peeters
Pathologische Ontleedkunde, K. U. Leuven,
Minderbroedersstraat 12,
3000 Louvain, Belgium

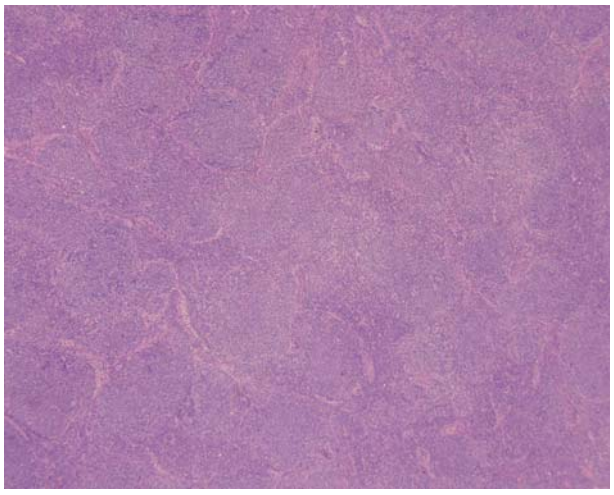

Fig. 1 The nodal architecture is effaced by numerous uniformly sized follicles that are closely packed together. These follicles lack mantle zones and are mostly composed of centrocytes

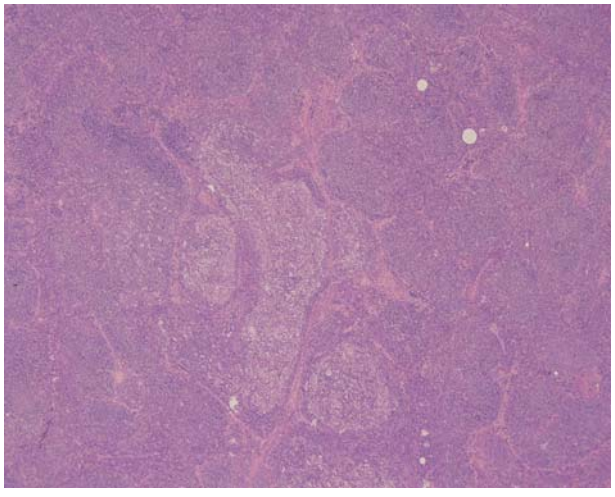

Fig. 2 Several nodules of larger size and featuring large atypical cells were found in a small area of the lymph node

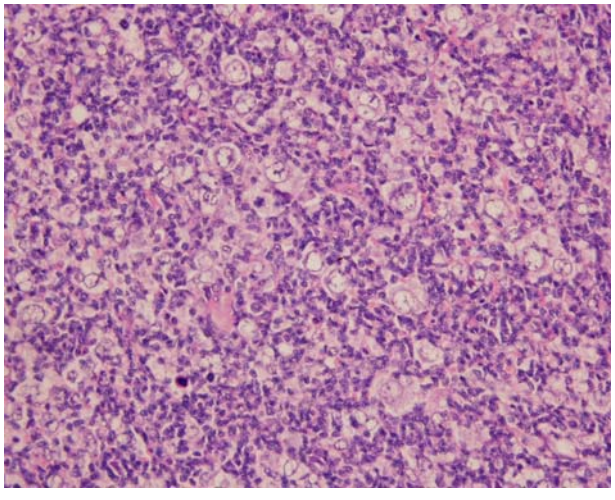

Fig. 3 The large atypical cells look like "pop corn" cells

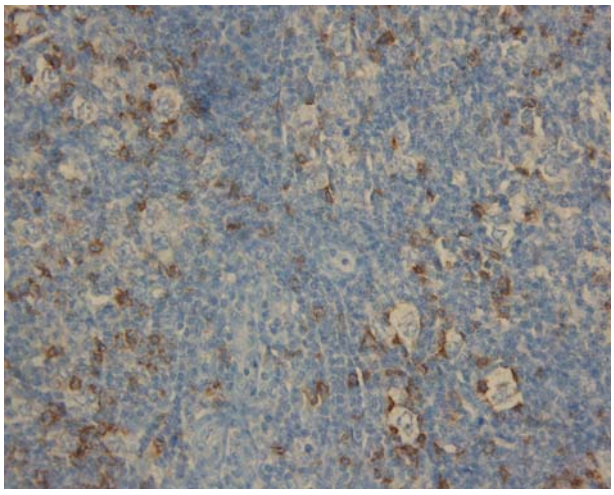

Fig. 4 Immunostaining with antibody directed against CD57. "Pop corn" cells are surrounded by CD57-positive lymphocytes

the bone marrow could be demonstrated. Six courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy were therefore given. The patient is in complete remission, 3 months after the end of therapy.

On rare occasions, CLs consisting of FL and classic Hodgkin's disease (HD) have been reported in the literature [4, 6–8, 10–12, 15, 16]. Using laser capture microdissection, PCR analysis, and sequencing of IgH gene rearrangements, a clonal relationship between the FL and HD has been demonstrated in some of these cases [4, 10, 12]. Interestingly, RS cells often express the bcl-2 protein or carry the t(14;18) translocation in these CLs [11, 12, 16]. To our knowledge, however, there has been no case report documenting the occurrence of FL and NLPHD within a single lymph node. Progression of NLPHD to diffuse large B cell lymphoma is a relatively well-known phenomenon [8], but the association with other B-cell lymphoproliferative disorders, in contrast with classic HD [5], is definitely unusual. Therefore, the present observation raises interesting questions about the relationship that might exist between FL and NLPHD. Unfortunately, we could not perform further molecular investigations in order to determine whether a clonal link between the "pop corn" cells and the FL cells does exist in our patient. Thus, we can only offer speculations on this issue. Nevertheless, two main possibilities may be considered, as follows.

At first, the NLPHD and FL components are totally unrelated and their occurrence together within the same lymph node simply represents a coincidental occurrence. In this regard, the absence of clonal relationship between the neoplastic components in some CL, like those involving HD and mantle cell lymphoma for instance [5], may support such a model of pathogenesis.

Second, both NLPHD and FL originate from a common precursor B cell, that is, the same abnormal B cell gives rise to the two neoplastic disorders through distinct maturation pathways in the germinal center (GC). In such a situation, the timing of t(14;18) translocation is of paramount im-

portance because this chromosomal anomaly is classically not involved in the pathogenesis of NLPHD [1]. Also, it was generally acknowledged that t(14;18) translocation takes place at the pre-B ontogenetic stage, during the initial phase of the IgH V region recombination process [13, 14]. However, recent studies have demonstrated that this chromosomal anomaly may arise at a later stage of B cell development, during receptor revision in the GC [13, 14]. Therefore, the possibility that a common precursor B cell first gives rise to NLPHD and thereafter to FL may be not so unreasonable. Moreover, the numerous similarities that exist between "pop corn" cells in NLPHD and GC B cells at the centroblastic stage of differentiation and the knowledge that FL cells may correspond to late centroblast or centrocyte GC B cells also are consistent with such a hypothesis [12, 14].

Due to differences in terms of prognosis, our case should be distinguished from FL showing progression to CD30-positive large cell lymphoma and from FL featuring numerous RS-like cells [2, 3]. In our patient, the phenotype of the "pop corn" cells as well as the presence of numerous CD57-positive T lymphocytes, notably around these cells, make such a progression unlikely and rather favor a diagnosis of CL featuring FL and NLPHD components. Interestingly, numerous small B lymphocytes in the large follicles harboring the "pop corn" cells were bcl-2 protein- and CD10-positive centrocytes, a finding that can be interpreted as colonization of these follicles by FL cells.

Whatever the precise pathogenesis may be, this intriguing observation further expands the spectrum of CL.

References

1. Algara P, Martinez P, Sanchez L, Villuendas R, Orradre JL, Oliva H, Piris MA (1991) Lymphocyte predominance Hodgkin's disease (nodular paragranuloma): a bcl-2 negative germinal centre lymphoma. Histopathology 19:69–75
2. Alsabeh R, Medeiros LJ, Glackin C, Weiss LM (1997) Transformation of follicular lymphoma into CD30-large cell lymphoma with anaplastic cytologic features. Am J Surg Pathol 21: 528–536
3. Bayerl MG, Bentley G, Bellan C, Leoncini L, Ehmann WC, Palutke M (2004) Lacunar and Reed–Sternberg-like cells in follicular lymphomas are clonally related to the centrocytic and centroblastic cells as demonstrated by laser capture microdissection. Am J Clin Pathol 122:858–864
4. Bräuninger A, Hansmann ML, Strickler JG, Dummer R, Burg G, Rajewsky K, Küppers R (1999) Identification of common germinal-center B-cell precursors in two patients with both Hodgkin's disease and non-Hodgkin's lymphoma. N Engl J Med 340:1239–1247
5. Caleo A, Sanchez-Aguilera A, Rodriguez S, Dotor AM, Beltran L, de Larrinoa AF, Menarguez FJ, Piris MA, Garcia JF (2003) Composite Hodgkin lymphoma and mantle cell lymphoma. Two clonally unrelated tumors. Am J Surg Pathol 27:1577–1580
6. Gonzalez CL, Medeiros LJ, Jaffe ES (1991) Composite lymphoma. A clinicopathologic analysis of nine patients with Hodgkin's disease and B-cell non-Hodgkin's lymphoma. Am J Clin Pathol 96:81–89
7. Hansmann ML, Fellbaum C, Hui PK, Lennert K (1989) Morphological and immunohistochemical investigation of non-Hodgkin's lymphoma combined with Hodgkin's disease. Histopathology 15:35–48
8. Jaffe ES, Zarate-Osorno A, Kingma DW, Raffeld M, Medeiros LJ (1994) The interrelationship between Hodgkin's disease and non-Hodgkin's lymphomas. Ann Oncol 5(suppl 1):7–11
9. Kim H (1993) Composite lymphoma and related disorders. Am J Clin Pathol 99:445–451
10. Küppers R, Sousa AB, Baur AS, Strickler JG, Rajewsky K, Hansmann ML (2001) Common germinal-center B-cell origin of the malignant cells in two composite lymphomas, involving classical Hodgkin's disease and either follicular lymphoma or B-CLL. Mol Med 7:285–292
11. Le Brun DP, Ngan BY, Weiss LM, Huie P, Warnke RA, Cleary ML (1994) The bcl-2 oncogene in Hodgkin's disease arising in the setting of follicular non-Hodgkin's lymphoma. Blood 83: 223–230
12. Marafioti T, Hummel M, Anagnostopoulos I, Foss HD, Huhn D, Stein H (1999) Classical Hodgkin's disease and follicular lymphoma originating from the same germinal center B cell. J Clin Oncol 17:3804–3809
13. Nadel B, Marculescu R, Le T, Rudnicki M, Böcskör S, Jäger U (2001) Novel insights into the mechanism of t(14;18)(q32;q21) translocation in follicular lymphoma. Leuk Lymphoma 42: 1181–1194
14. Stamatopoulos K, Kosmas C, Belessi C, Stavroyianni N, Kyriazopoulos P, Papadaki T (2000) Molecular insights into the immunopathogenesis of follicular lymphoma. Immunol Today 21:298–305
15. Thirumala S, Esposito M, Fuchs A (2000) An unusual variant of composite lymphoma. A short case report and review of the literature. Arch Pathol Lab Med 124:1376–1378
16. Urano M, Mizoguchi Y, Nishio T, Abe M, Kuroda M, Saito S, Sakurai K (2004) Composite lymphoma arising in the parotid gland: a case report. Auris Nasus Larynx 31:89–93