Eur J Cancer Clin Oncol, Vol. 23, No. 5, pp. 465–467, 1987.
Printed in Great Britain

0277-5379/87$3.00+0.00
Pergamon Journals Ltd.

Perspectives and Commentaries

Hairy Cell Leukemia Still an Enigmatic Disease

JAN JANSEN

Divison of Hematology/Oncology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IA 46223, *U.S.A.*

(A COMMENT ON: Viero P, Cortelazzo S, Barbui T, Semararo N. Generation of procoagulant activity by hairy cells in response to endotoxin and phorbol esters. *Eur J Cancer Clin Oncol* 1986, **22**, 857–862.)

HAIRY cell leukemia (HCL), also known as leukemic reticuloendotheliosis, has been the subject of debate ever since its first description as a separate clinical pathologic entity in 1958. Bouroncle *et al.* reported a series of patients who presented with splenomegaly without lymphadenopathy, and mostly with pancytopenia. In the peripheral blood and bone marrow, cells with an indistinct, serrated or hairy, cell border were found. These cells eluded easy classification, and the authors considered them to be very immature reticulum cells [1]. Hence, the name leukemic reticuloendotheliosis. Later on, most investigators favored the more descriptive name hairy cell leukemia over leukemic reticuloendotheliosis, although both are still being used interchangeably. The disease seems to have attracted more interest than can merely be attributed to its incidence; HCL accounts for only approximately 2% of all leukemias. This interest can be partly explained by the ongoing difficulties in precisely classifying the origin of the neoplastic cells, and by the recent demonstration of the extreme sensitivity of the disease to treatment with one of the first biologic response modifiers, i.e. interferon.

On the basis of morphology, hairy cells (HC) were assigned to either the lymphocytic or monocytic lineage. Some investigators claimed a "hybrid" position between the two lineages for these cells. Technical pitfalls often made the interpretation of cell surface features hazardous. In particular, the stickiness of the cell membrane of HC and the presence of avid receptors for the Fc-part of IgG frequently caused confusion when studies with polyclonal or monoclonal antisera against cell surface structures were performed. In addition, the serrated cell border made interpretation of phagocytosis by HC, one of the main arguments for a monocytic origin, hazardous. Several groups, each studying a fair number of cases and applying different techniques to circumvent the technical pitfalls, found that the HC of most cases exhibit intrinsic surface immunoglobulins (SIg) [2–4]. The SIg is monoclonal as far as light-chain composition is concerned, but, interestingly, often multiple heavy-chain determinants are present [2, 4]. The presence of intrinsic SIg, and in a small minority of cases the presence of cytoplasmic immunoglobulin and/or the production of an M-protein, is compelling evidence for the B-cell origin of HCL. More recently the reactivity of HC with monoclonal antibodies against B lymphocytes, has corroborated the concept that HC are indeed neoplastic B cells [5, 6]. Even more convincingly, recombinant-DNA technology has shown that the imunoglobulin genes in HC have rearranged in such a way that messenger RNA can be assembled to initiate immunoglobulin production [7]. The combination of these features can leave little doubt that HCL constitutes a B-lymphocytic neoplasm. Attempts have been made to localize the "maturation arrest" of HCL as it compares to chronic lymphocytic leukemia and other B-cell leukemias. The SIg is often of IgG-class, or has multiple heavy-chain determinants. This would locate HCL as more mature than chronic lymphocytic leukemia or prolymphocytic leukemia [2, 4]. Similarly, the reactivity pattern with monoclonal antibodies suggests that HCL is more mature than chronic lymphocytic leukemia. Thus, HC react with monoclonal antibodies of cluster of differentiation (CD)19 (Leu-12, B4), with antibody FMC7, and

Accepted 30 July 1986.

with plasma cell related antibodies PCA-1 and PC-1, but not with antibodies of CD5 (Leu-1, T101) [5, 6, 8, 9]. It is noteworthy that HC also react with antibodies of CD25, which represent the receptor for interleukin-2 [7], and CD11 (OKM1,Mo-1) which recognize a monocyte-granulocyte antigen [5, 6, 8, 9]. Reactivity with CD25 and CD11 has also been reported for other mature B-cell leukemias such as prolymphocytic leukemia [9].

If HCL constitutes such a definite B-cell malignancy, why then is there still controversy and is its association with monocytes still being suggested? The answer is that again and again functional features of HC are being found that are not compatible with the B-cell lineage, but are associated with cells of monocytic origin. In their paper, Viero *et al.* report that HC respond to exposure to endotoxin and/or phorbol-ester (TPA) with the formation of procoagulant activity [10]. Such activity is being found in monocytes and promyelocytes, but usually not in cells of lymphocytic lineage. How can the presence of a functional activity so unusual for lymphocytes be explained in HC which otherwise have all the characteristics of neoplastic B-cells? A number of possibilities exist. First, HCL could truly represent a neoplasm of "hybrid" cells between B lymphocytes and monocytes. Since, at least *in vitro*, B lymphocytes and monocytes branch off at very different stages of hematopoietic progenitor cell commitment [11], this possibility seems rather remote. Secondly, normal B lymphocytes at a certain stage of their differentiation may possess the capability to produce procoagulant activity. This would be in line with the concept that HC represent the neoplastic counterpart of a rather rare, activated, stage of B-cell differentiation [12]. In this respect, it would be very interesting to study other chronic B-cell leukemias which represent rather mature stages of differentiation, such as prolymphocytic leukemia and lymphoplasmacytoid leukemia [9] for the inducibility of procoagulant activity. Thirdly, the capability to generate procoagulant activity may be part of the malignant transformation of hairy cells. Indeed, very little is known yet about the activation of oncogenes in HCL.

For the time being, it seems most attractive to explain the inducibility of procoagulant activity as a marker of a certain rare and/or short lived stage of normal B-cell differentiation. This would place the phenomenon in the same category as the presence of monocyte-associated CD11 and activated T-cell associated CD25 on the cell surface membrane of HC and closely related chronic B-cell leukemias [5, 9]. This stage is probably associated with a high degree of activation, as documented by the presence of interleukin-2 receptors [13] and reactivity with antibody HC2 [12]. This activation in turn could lead to a highly active, serrated, and sticky cell membrane, and to the induction of new proteins, of which tartrate-resistant acid phosphatase [14] and possibly procoagulant activity are just two examples. This state of activation may also explain why interferon, which has shown only limited effect in other B-cell neoplasms, is so uniquely effective in HCL [15]. This biologic response modifier has proven to cause dramatic improvement in the majority of patients with progressive HCL, and even occasionally to induce complete remission. It has to be determined whether this striking beneficial response is caused by a direct cytotoxic effect, or through the induction of HC to a more mature, probably resting, stage.

Almost 30 years have gone by since HCL was first reported as a separate entity. Much has been learned in the meantime about the clinical features, the immunology, and the therapeutical options. Nevertheless, unique features of HC continue to be reported and make the disease as enigmatic as ever.

REFERENCES

1. Bouroncle BA, Wiseman BK, Doan CA. Leukemic reticuloendotheliosis. *Blood* 1958, **13**, 609–630.
2. Burns GF, Cawley JC, Worman CP *et al.* Multiple heavy chain isotypes on the surface of the cells of hairy cell leukemia. *Blood* 1978, **52**, 1132–1147.
3. Golomb HM, Vardiman J, Sweet Jr DL, Simon D, Variakojis D. Hairy cell leukaemia: Evidence for the existence of a spectrum of functional characteristics. *Br J Haemat* 1978, **38**, 161–170.
4. Jansen J, Schuit HRE, Meijer CJLM, van Nieuwkoop JA, Hijmans W. Cell markers in hairy cell leukemia studied in cells from 51 patients. *Blood* 1982, **59**, 52–60.
5. Jansen J, LeBien TW, Kersey JH. The phenotype of the neoplastic cells of hairy cell leukemia studied with monoclonal antibodies. *Blood* 1982, **59**, 609–614.
6. Janckila AJ, Stelzer GT, Wallace JH, Yam LT. Phenotype of the hairy cells of leukemic reticuloendotheliosis defined by monoclonal antibodies. *Am J Clin Pathol* 1983, **79**, 431–437.
7. Korsmeyer SJ, Greene WC, Cossman J *et al.* Rearrangement and expression of immunoglobulin genes and expression of Tac antigen in hairy cell leukemia. *Proc Natl Acad Sci USA* 1983, **80**, 4522–4526.

8. Anderson KC, Boyd AW, Fisher DC, Leslie D, Schlossman SF, Nadler LM. Hairy cell leukemia: A tumor of pre-plasma cells. *Blood* 1985, **65**, 620–629.
9. Den Ottolander GJ, Schuit HRE, Waayer JLM, Huibregtsen L, Hijmans W, Jansen J. Chronic B-cell leukemias: relation between morphological and immunological features. *Clin Immunol Immunopath* 1985, **35**, 92–102.
10. Viero P, Cortelazzo S, Barbui T, Semeraro N. Generation of procoagulant activity by hairy cells in response to endotoxin and phorbol esters. *Eur J Cancer Clin Oncol* 1986, **22**, 857–862.
11. Ogawa M, Porter PN, Nakahata T. Renewal and commitment to differentiation of hemopoietic stem cells (an interpretive review). *Blood* 1983, **61**, 823–829.
12. Posnett DN, Wang C, Chiorazzi N, Crow MK, Kunkel HG. An antigen chracteristic of hairy cell leukemia cells is expressed on certain activated B cells. *J Immunol* 1984, **133**, 1635–1640.
13. Muraguchi A, Kehrl JH, Longo DL, Volkman DJ, Smith KA, Fauci AS. Interleukin 2 receptors on human B cells. Implications for the role of interleukin 2 in human B cell function. *J Exp Med* 1985, **161**, 181–197.
14. Lam K, Yam LT. Biochemical characterization of the tartrate-resistant acid phosphatase of human spleen with leukemic reticuloendotheliosis as a pyrophosphatase. *Clin Chem* 1977, **23**, 89–94.
15. Quesada JR, Reuben J, Manning JT, Hersh EM, Gutterman JM. Alpha-interferon for induction of remission in hairy-cell leukemia. *N Engl J Med* 1984, **310**, 15–18.