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Lymphoma and Leukemia Cells Possess Fractal Dimensions That Correlate with Their Biological Features

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Key Words
Cell phenotype · Chaos theory · Complex adaptive systems · Fractal dimension · Hematological malignancies · Non-linear dynamics

Abstract
Background: Living cells can be viewed as complex adaptive systems that exhibit non-linear dynamics and fractal features. We investigated the fractal qualities of normal and malignant hematological cells and their potential as a tool for characterizing cell phenotype and clinical behavior. ***Methods:*** A mathematical algorithm and an optic tool for fractal analysis of nuclei were developed. A total of 4,713 lymphoid cells derived from 66 patients of five distinct diagnostic groups (normal and reactive lymphocytes, low-grade lymphomas and an aggressive lymphoma) were assessed for their fractal dimension. In addition, in 19 patients fractal analysis of leukemia cells was compared to clinical endpoints. ***Results:*** After validating our method, hematological cells possessed fractal dimensions corresponding to their clinical entity. There was a highly significant overall difference in fractal dimensions between various types of hematological malignancies. A preliminary correlation was found between the fractal dimension and the clinical outcome of leukemia patients. ***Conclusions:*** Hematological cells possess fractal dimensions that correlate with their biological properties. Measurement of fractal dimension seems to be a sensitive method to assess the hematological cell phenotype and to define a clinical group. This tool may be potentially useful for the evaluation of clinical behavior of hematological diseases.

Introduction

Cancer is currently viewed as a complex and robust biological system [1]. Human cell function, whether normal or malignant, is a result of numerous interactions between various effectors that result in a functioning, stable biological system. In order for such a complex system to maintain stability despite various perturbations, the system must have a high degree of robustness. Such robustness is achieved by various traits such as adaptation and tolerance to stochastic fluctuations which are enabled by feedback control, redundancy, modularity

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and structural stability tactics [1]. Malignant transformation is classically viewed as a multistaged process characterized by accumulation of genetic alterations that eventually lead to the creation of a clone of cells that proliferate relentlessly [2]. The phenotype of the malignant cell is the result of multiple interactions between various effectors and processes within the affected cell and its environment. Thus, the malignant biological system can be best characterized as a complex adaptive system. In complex adaptive systems, the abundance of inputs, variables and processes, and complexity of interactions that influence the output are best described by non-linear dynamics. This method is used to mathematically describe various systems from different disciplines such as ecology (including weather systems), astronomy and, recently, many biological systems. Unlike simple linear systems in which prediction of an output according to an input is relatively simple, it is very hard to predict the response of the complex system even to a simple input. In the face of the overwhelming importance of predicting the behavior of such complex systems, new mathematical approaches have been adopted in an effort to acquire predictive tools. One such tool is the deterministic chaos theory. This theory, also known simply as chaos theory, is the mathematical description of complex behavior that arises from subtle changes in non-linear systems [3]. One of the descriptive tools that are used to address complex, non-linear chaos-dynamic systems is fractal geometry. A fractal is the visual product of the chaotic non-linear system and is characterized by its complexity and by the quality of self-similarity or scale invariance [3]. Fractal-like patterns are seen in human tissue as well and has been used to describe nerve networks, vascular networks and many other biological systems [4–7]. When applying fractal geometry to describe complex biological systems we address the statistical fractal image which is apposed to the true mathematical fractal image and applies to a system that possesses qualities of complexity and self-similarity to such an extent that allows us to use fractal geometry to describe it. The fractal dimension is an index of the space filled by the fractal structure and is a mathematical expression that indicates the chaotic level of the system assessed and the extent of complexity and self-similarity of the system.

The implementation of the deterministic chaos theory and of fractal geometry in complex biological systems has been described in various studies in recent years [4, 5, 8, 9].

Seeking chaotic features in cell biology, in tumorigenesis and in malignant cells has been attempted in the past. Cells have been shown to possess a fractal dimension reflecting their complexity and their self-similarity qualities. Complexity is reflected in numerous variables, processes and interactions creating non-linear dynamics in cell biology. Self-similarity has been shown to exist among cell subunits and organelles and by scanning cell membrane and cell nucleus membrane 'coastlines' at different magnifications and showing similarity in form between the different scales [10, 11]. Observing the cell as a complex adaptive system in relation to the malignant transformation where a relatively small measurable input such as a genetic mutation may have an immense impact on cell phenotype correlates with chaotic behavior.

Lymphomas and leukemias are a group of heterogeneous diseases that differ in biological and clinical behavior. The diagnosis and classification of the different types of malignancies is based on the phenotypic description of the malignant cell using the morphologic description and immunohistochemical markers. Frequently, patients with pathologically similar disease manifest heterogeneous biological and clinical behavior. The diffuse large B cell lymphoma (DLBCL) is an example for the above-stated points. Based on morphologic and clinical criteria, DLBCL is considered a single category and as a consequence all patients receive the same therapy. However, the response to multi-agent chemotherapy is very heterogeneous. Recent gene expression profiling has shown that the DLBCL diagnostic category consists of at least three subgroups that differ from each other by gene expression and are distinct entities from the survival viewpoint [12]. Thus, with currently available tools the ability to guide diagnosis and treatment of lymphoma and leukemia is not satisfactory and we should strive to develop new tools that will better predict the clinical behavior of these diseases. We propose that normal hematological cell and malignant hematological cells can be viewed as complex adaptive systems. Determining whether they obey the rules of deterministic chaos and carry a fractal dimension can assist us in better understanding their phenotype and help us in more precisely predicting biological and clinical behavior.

In this study, we attempted to develop a mathematical algorithm and an optic tool for identifying normal and malignant hematological cell nucleus 'coastlines' and calculate their fractal dimensions, thereafter assessing whether these cells are actually fractal objects that possess a scale-invariable self-similarity quality. We then asked whether there is a correlation between the fractal dimensions and the biological behavior of lymphoma by comparing fractal dimensions of cells from different

types of lymphomas. Finally, we conducted a preliminary assessment of correlation between fractal dimensions and clinical outcome in a small group of patients with acute leukemia.

Materials and Methods

Optic Tools, Mathematical Algorithms and Work Process

A mathematical algorithm and an optic tool by which images could be captured and have their fractal dimension calculated was developed. Pathological samples were photographed using an Olympus BX51 microscope set to ×100 magnification equipped with an Olympus DP50 digital camera and View Finder software. Each image had a resolution of 2,400 × 1,600 pixels. The images were saved as 8-bit grayscale files in a tagged image file format (.tif). K-means clustering algorithm was applied on all captured images. The image was segmented to four clusters according to gray values. The binary segmented result was a combination of the three clusters with low cluster centers correlating to low gray values. One of the advantages of using K-means clustering is that it adaptively thresholds the image and removes the background, so the foreground will contain only the cells. Each image contained only a single cell, following manual cropping. Cells that were crossed by the image borders were removed automatically. For each sample evaluated, a digital picture was obtained from ten different fields chosen randomly. For each image acquired, a color calibration procedure was applied so that the value of absolute white and absolute black would be identical for all samples. From these samples, cells that do not overlap with other cells were chosen and each of these cells was saved as a single file.

For each image, a fractal dimension, Df, was calculated using the modified box-counting method (MBCM). In this method the image evaluated is put on a grid of squares that possess an r limb length, whereafter the number of squares that are required to cover the image (e.g. that possess black dots) are counted (N). This process is repeated for increasing r-values and the fractal dimension, Df, can then be calculated using the formula:

$$Df = \lim \frac{\log(N)}{\log(1/r)}$$

We also created a function where the x-axis values are defined by log (*N*) and the y-axis values are defined by log (1/*r*). A linear slope of the graph would then express the fractal dimension, Df. A nonlinear slope would imply a lack of fractal dimension.

The slope of the graph can be calculated using the formula:

$$Df = \left(\frac{n\sum xy - \left(\sum x\right)\left(\sum y\right)}{n\sum x^2 - \left(\sum x\right)^2} \right)$$

where x = log(*N*) and y = log(1/*r*).

The MBCM is different from the traditional box-counting method due to two improvements introduced by Buczkowski et al. [13] aimed at reducing errors in the calculation of fractal dimensions:

(1) The value for the square limb length chosen, r, affects the Df calculated. Using extreme r values approaching 1 or approaching the whole image length can influence the Df slope. Repeated identical N values for different r values chosen will also influence the Df slope. For all of these reasons, r values are restricted to the following:

$$\left\{ r \middle| 3 < r < \frac{L}{2} \right\}$$

with *L* being defined as the whole image length.

(2) The position of the different square grids applied on the image assessed will influence the Df calculated if different starting points for each grid positioning will be used. Buczkowski et al. [13] have introduced a solution to this problem: x_{min} of the image is defined as the smallest width point where a black pixel exists. x_{max} is defined as the largest width point where a black pixel exists. The same definitions apply to y_{min} and y_{max} regarding length values. Then the square grid can be applied in the range:

$$\{(x, y) \mid (x_{min}, y_{min}) - (x_{max}, y_{max})\}$$

The described MBCM algorithm was implemented in Mathworks Matlab.

In an attempt to validate the described method, it has first been applied to geometrical objects without a fractal dimension (line, square and circle) and then to geometrical fractal objects.

Lymphoid Cell Acquisition and Fractal Assessment

In order to calculate dimensions of lymphoid cells, samples of lymph nodes were evaluated. We assessed archival pathological slides which were prepared using standard clinical methods of 6 normal lymph nodes, 10 reactive nodes, 11 samples from chronic lymphatic leukemia (CLL) patients, 21 follicular lymphoma samples and 18 DLBCL samples. All samples were randomly collected, were anonymous and were coded by the pathologist.

The above-described method was then used to calculate the dimension of the lymphocytes from the lymph node biopsies. We counted an average of 71 cells per patient sample.

Leukemia Cell Acquisition, Leukemia Clinical Scoring and Fractal Assessment

A preliminary attempt to assess whether fractal dimension correlates with clinical behavior was made. Bone marrow biopsies from 19 patients diagnosed with acute myeloid leukemia (AML) were inspected. All samples were obtained at diagnosis from 1999 to 2001, and clinical data were obtained from the patients' files. Fractal dimensions were calculated on 30 leukemic cells per patient. In order to correlate between the fractal dimension leukemia cells and clinical phenotype, we classified patients into two groups: those with a 'good' and a 'bad' outcome. 'Good clinical behavior' was defined as patients who achieved complete remission after induction chemotherapy and survived for 2 years after diagnosis. All other patients were defined as 'bad-risk patients'. In an attempt to check solely the association between clinical course and leukemic cell fractal dimensions, we did not include the standard risk stratification (chromosomal and molecular data).

Statistical Analysis

One-way analysis of variance was used in order to calculate the overall statistical difference between the different groups of lymphocytes assessed. Post hoc Tukey test was used to evaluate the presence of statistical significance between adjacent groups.

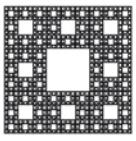
Object		Theoretical fractal dimension	Calculated fractal dimension	
Straight line		1	0.98	Non-fractal geometrical objects
Circle		1	1.02	
Empty square		1	1.06	
Filled square		2	1.998	
Sierpinski carpet		1.892	1.896	Fractal geometrical objects
Sierpinski gasket		1.565	1.589	

Fig. 1. Calculated dimensions of mathematical fractal and non-fractal objects compared with their theoretical dimensions.

Cluster analysis was used in order to identify the different subgroups in the DLBCL group. ANOVA was used to assess the significance of these findings. Statistica software was used for all statistical analysis.

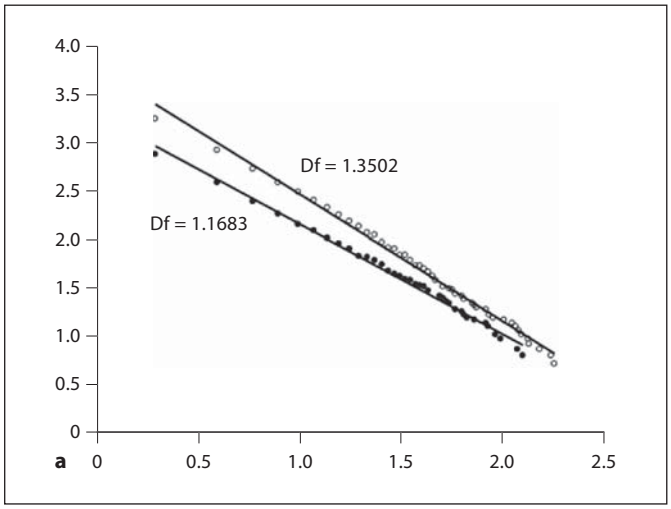
Results

The dimensions calculated by our method were similar to the theoretical dimensions of the tested geometrical objects. The accuracy of calculation was shown both in non-fractal (line, square and circle) as well as in fractal (Sierpinski gasket and Sierpinski carpet) objects (fig. 1).

After validation of the method for capturing cell images and calculating their fractal dimension, we addressed the question whether lymphocytes possess fractal dimensions. Representative results are depicted in figure 2. Figure 2a represents the results of normal lymphocytes and DLBCL cells. A power-law linear relationship was demonstrated, implying that normal and malignant lymphatic cells possess a fractal dimension. Similar results were obtained with CLL cells (fig. 2b) and other lymphomas. The average R^2 value was 0.98 (range 0.962–0.995).

Table 1. Diagnostic characterization of the different groups sampled, number of patients and cells sampled of each group

Type	Total patients	Total cells	Cells/ patient
Normal lymph nodes	6	658	109.67
Reactive lymph nodes	10	939	93.90
CLL	11	932	84.73
Follicular lymphoma	21	1,524	72.57
DLBCL	18	660	36.67
Total	66	4,713	71.41



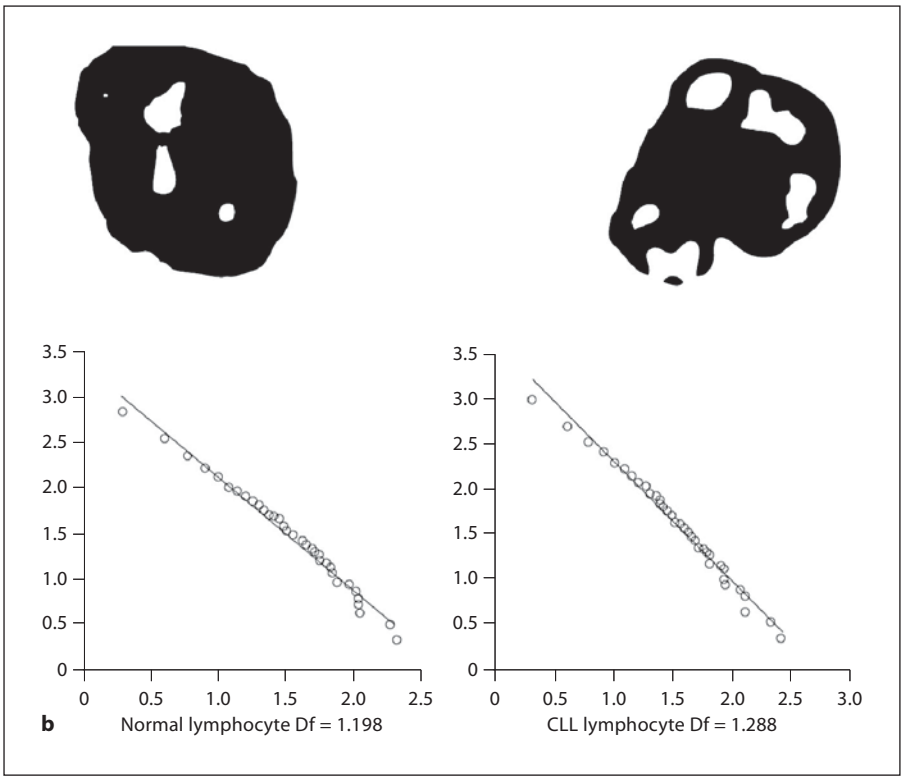


Fig. 2. Both normal and malignant cells possess a fractal dimension. **a** Filled dots: normal lymph node. Circles = DLBCL. Dot scattering pattern reveals a power-law relationship implying that lymphatic cells possess a fractal dimension. **b** Normal lymphocyte nucleus versus a lymphocyte nucleus of patients with CLL; the cell nucleus outlining two cell types are displayed above. The dot scattering pattern below reveals a power-law linear relationship from which the fractal dimension is calculated. Note that despite the visual resemblance between the cell nuclei, fractal dimensions are significantly different. The average R^2 value was 0.98 (range 0.962–0.995).

In order to assess the relationship between biological features of the cells and their fractal dimensions we calculated fractal dimensions on lymphatic cells from various sources: normal and reactive lymph nodes, indolent lymphoma (CLL and follicular lymphoma grade 1–2) and aggressive lymphoma (DLBCL). An average number of 71 cells were counted in each sample (table 1).

Figure 3 shows fractal dimension of normal lymphocytes, reactive lymphocytes and cells of CLL, follicular lymphoma and DLBCL. There was an overall highly significant difference between the fractal dimensions of all groups as calculated using ANOVA ($p < 0.005$, $F = 5.72$). It can be seen that low-grade malignancies (CLL and follicular lymphoma) clustered together. Reactive lymphocytes were situated between CLL and normal cells, while

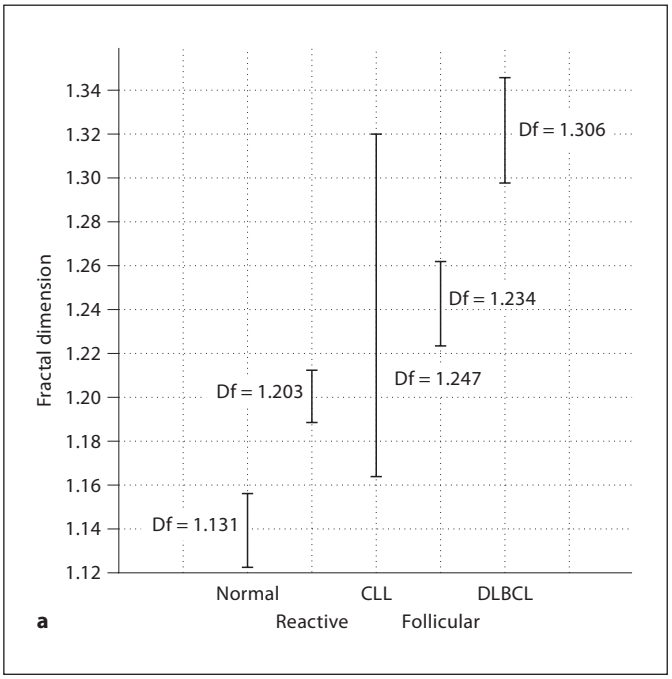


Fig. 3. a Fractal dimensions of lymphocytes from various diagnostic groups. A high overall significance was demonstrated between the adjacent groups using ANOVA ($p < 0.005$, $F = 5.72$). **b** Average fractal dimension of different diagnostic groups. **c** Post hoc analysis comparing the different groups.

	No. patients	Average cells per patient	Df (average between patients)	Min Df	Max Df	Std Dev
Normal lymph nodes	6	109.67	1.131	1.1123	1.156	0.015
Reactive lymph nodes	10	93.9	1.203	1.189	1.212	0.005
CLL	11	84.73	1.247	1.164	1.32	0.207
Follicular lymphoma	21	72.57	1.234	1.223	1.265	0.013
DLBCL	18	36.67	1.306	1.298	1.345	0.012

b

Groups	p value
Normal vs. reactive	0.47
Normal vs. CLL	0.066
Normal vs. follicular	0.07
Normal vs. DLBCL	<0.0005
Reactive vs. CLL	0.76
Reactive vs. follicular	0.86
Reactive vs. DLBCL	0.024
CLL vs. follicular	0.99
CLL vs. DLBCL	0.36
Follicular vs. DLBCL	0.079

c

aggressive lymphoma cells had a significantly higher fractal dimension. The post hoc Tukey test revealed a significant difference when comparing the DLBCL with normal and reactive lymph nodes.

Further analysis was performed within the DLBCL group. Intra-group distribution among the DLBCL study group was assessed using the cluster analysis method. This analysis revealed a distribution into three distinct subgroups based on their fractal dimension. ANOVA has shown statistical significance between these subgroups ($p < 0.0001$; fig. 4).

In order to evaluate the possible clinical significance of fractal dimensions of malignant cells, we studied 19 patients with AML treated 3 years earlier. We have calculated the fractal dimension of these patients' cells and looked for intra-group distribution. The analysis demonstrated apparent distinct subgroups. One group contained 5 patients, all of them good responders according to the before-mentioned criteria. The second group contained 14 patients; 4 of them demonstrated good clinical response, while the remainder were poor responders. Thus, grouping the AML patients by fractal dimensions

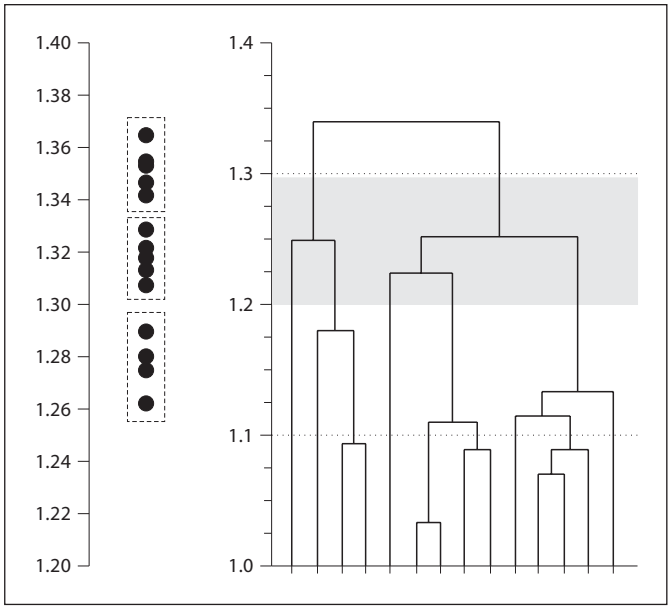


Fig. 4. Distribution of the DLBCL diagnostic study group into three subgroups based on their fractal dimension. On the right: tree joining cluster analysis of the fractal dimension, where the gray strip indicates the turning point of statistical distribution into the three distinct subgroups. On the left hand: distribution into three subgroups as shown by cluster analysis. A broken line delineates each distinct subgroup. y-axis represents the fractal dimension. ANOVA revealed statistical significance between these subgroups ($p < 0.0001$).

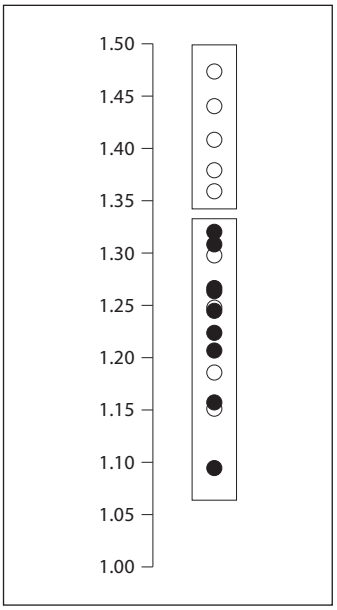


Fig. 5. Fractal dimension and clinical response in AML patients. ○ = Patients with good clinical response; ● = patients with poor clinical response. A line delineates the two distinct subgroups with 100%, and a 28% rate of good clinical response is demonstrated in the upper and lower groups, respectively.

may distinguish between a group with a good response rate (100%; 5/5) and a second group with a standard response rate of 28% (4/14), which is the accepted response rate for AML. These results are descriptive and preliminary, and obviously require reproduction in a larger patient cohort (fig. 5).

Discussion

Human cells can be viewed as biological complex adaptive systems and therefore possess a non-linear relationship and challenge the traditional research methodologies that assume a well-defined, linear relationship in the investigated models. Recognizing the non-linearity and complexity of biological systems and the unpredictability of the genotype-phenotype relationship has led to a quest for new tools by which characterization and prediction of complex system behavior can be achieved. The use of the deterministic chaos theory and fractal dimensions as a descriptive and predictive tool to characterize biological complex adaptive systems can be utilized in order to achieve better understanding of these systems. The importance of gaining the ability to describe and predict complex biological behavior is of special significance when dealing with malignant cells and cancer systems as it can deepen our understanding of these processes and aid to diagnosis and treatment.

Although our knowledge of lymphomas and leukemias encompasses their various genetic aberrations and their distinct morphologic features, we use different clinical scoring systems to predict their biologic behavior. Furthermore, we still lack the ability to adequately predict the clinical behavior of these diseases based on phenotypic description alone. In this study, we attempted to develop a mathematical algorithm and an optic tool and technique for identifying normal and malignant hematological cell nucleus 'coastlines' and calculate their fractal dimension thereafter assessing whether these cells are actually fractal objects that possess a scale-invariable self-similarity quality. After validating our work process by applying our algorithm and an optic tool on well-recog-

nized fractal and non-fractal geometrical objects, we have shown that hematological cells possess a fractal dimension by demonstrating power-law relationship for all cells evaluated.

We compared fractal dimensions between normal lymphoid cells, reactive lymphoid cells and different lymphoid malignant cells and demonstrated that lymphoid cells that belong to different diagnostic groups possess different fractal dimensions. It should be stressed that cells that had a similar morphometric appearance possessed different fractal dimensions according to their diagnostic ascription. This finding strengthens our assumption that the fractal dimension reflects the sum of interactions leading to the cell phenotype. Sedivy et al. [11] previously demonstrated that human cells have fractal dimensions in dysplastic and control nuclei derived from uterus cervix cone biopsies. Thus, our findings are consistent with previous reports [11, 15]. It is worth pointing out that there was a correlation between the fractal dimension and the aggressiveness of the lymphoma, i.e. the more aggressive the lymphoma, the higher the fractal dimension. While normal lymph node cells possessed an average Df of 1.131 and reactive lymph node cells possessed an average Df of 1.203, CLL, follicular lymphoma and DLBCL cells possessed an average Df of 1.247, 1.234 and 1.306, respectively. Ivanov et al. [9] suggested that a higher degree of chaos, as expressed by a higher fractal dimension, reflects the intact, equilibrated function of a complex biological system. They have shown in their work that the human heartbeat is a highly chaotic system and has also shown that the multifractal structure of healthy dynamics is lost with congestive heart failure. Goldberger et al. [8] further demonstrated higher regularity and altered fractal scaling associated with physiological aging and senescence of the body systems consistent with a loss of complex variability [8, 16]. Seemingly, our findings do not correlate with the above-stated points as we demonstrated that fractal dimension increases as the disease is more aggressive. One way to settle this apparent contradiction is keeping in mind that aggressive lymphomas have better clinical outcomes and cure rates than indolent lymphomas. It is noteworthy that Sedivy et al. [11] demonstrated similar findings showing correlation between the degree of uterus cervix dysplasia (cervical intraepithelial neoplasia I–III) and fractal dimension.

An interesting finding in our study was the disclosure of three fractal-associated subgroups of DLBCL using cluster analysis. This finding is of special interest in the face of recent gene expression profiling techniques that have shown that the DLBCL diagnostic category consists of at least three gene expression subgroups that differ from each other in their genetic, molecular and clinical aspects (germinal center B-cell like, activated B-cell like and type 3). Further study is required in order to conclude whether these fractal-associated DLBCL subgroups demonstrate distinct biological and clinical behavior and whether there is a correlation between the fractal-associated DLBCL subgroups and the gene-expression-derived DLBCL subgroups. This preliminary finding may be an example for the apparent sensitivity of the fractal analysis compared with the conventional phenotype descriptive methods used today. The last phase of our study was a preliminary attempt to seek correlation between fractal dimension and clinical behavior of leukemia. In our study, malignant AML cells derived from bone marrow biopsies of 19 patients assessed for fractal dimension seem to breakdown into two distinct groups by fractal dimension. In one group, a good clinical response of 100% (5/5 patients) was observed compared with a 28% good clinical response (4/14 patients) observed in the second group. Clinical response was based on response to treatment and 2-year survival alone, ignoring all other phenotypic and genotypic properties of the leukemia. The latter group demonstrated the accepted survival rate amongst AML patients, while the former group demonstrated exceptionally high good clinical response. The good clinical response group had a significantly higher calculated fractal dimension than the poor clinical response group correlating with our speculation that a higher fractal dimension is a sign of a healthier, well-equilibrated biological system. According to these preliminary findings, we speculate that fractal characterization of malignant cell phenotype can predict clinical behavior to some extent. Since these results are descriptive and are based on a small number of leukemia patients, further verification of these results is needed.

In a related study, Adam et al. [15] calculated the fractal dimension of nuclear chromatin (using the Minkowski-Bouligand method extended to three dimensions) of blasts derived from 28 patients with acute B lymphoblastic leukemia and assessed its prognostic importance. While fractal dimension had no prognostic importance in that study, goodness of fit of the fractal dimension, estimated by R^2, correlated with prolonged survival.

The main limitation of this study is a relatively small number of patients studied. Therefore, the results should be viewed as proof of concept and as preliminary data requiring further confirmation. We are currently in pro-

cess of verifying these results on much larger cohorts of patients with hematological malignancies.

This study is part of an emerging scientific trend towards viewing biological systems as complex adaptive systems and offers descriptive and predictive tools in order to address this evolving challenge. In addition, our work offers an additional simple, rapid and non-expensive tool for evaluating the prognosis and treatment of patients with hematological malignancies. In the future, this method could be utilized for risk stratification of hematological malignant disorders. More studies are needed to deepen our understanding of the relationship between the malignant cell fractal dimension and the malignant cell phenotype. Further, the correlations between fractal and molecular properties of the malignant cells and clinical behavior should be further studied.

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