Should clinical hematologists put their microscopes on eBay?

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Since Dimitri Romanowski, in 1891, invented a staining technique that made intracellular structures visible, and Gustaaf Giemsa, in his studies of malaria detection, described a method to stabilize and standardize this technique, light microscopic examination and description of the cells on films of blood and bone marrow has been the most important tool in the diagnosis and classification of hematologic malignancies.[1,2] Subsequently, in 1976, this morphological assessment formed the basis of the French-American-British (FAB) classification.[3] To define the lymphatic, myeloid and monocytic character of the cells more specifically than the degree obtained using only morphology, cytochemical reactions for myeloperoxidase and non-specific esterase, also performed on the film, were included. Soon immunological methods were added to this classification for the detection of megakaryoblasts and those blasts that are negative both for myeloperoxydase and B- and T-lymphoid markers.[4,5]

The introduction of the immunophenotypic characterization of the cells for diagnostic purposes was further facilitated when monoclonal antibodies and flow cytometric reading techniques became available in the 1980s. In those days, the immunophenotypic characterization of hematologic malignancies was considered by many to generate much more objective results than morphology.

But a new development, starting with the discovery of the Philadelphia chromosome in 1960 and the underlying translocation (9;22) in 1973, led to the definition of the disease entity of chronic myeloid leukemia, primarily based on a genetic abnormality.[6,7] Acute myeloid leukemias with recurrent cytogenetic abnormalities were to follow (WHO 2001) and also mutations themselves became the key defining criterion (WHO 2008).[8,9] This development is expected to progress further when new generation sequencing will become daily diagnostic practice.[10]

Without a doubt, these developments have changed the role and significance of the morphological profile in the diagnosis of hematologic malignancies considerably, and will continue to do so in the future.

But should we, as clinical hematologists, sell our microscopes on eBay?

Let us not be too quick to say "no". Although the question is a painful one (because one of the most attractive aspects of hematology, and the reason why many physicians choose to become a clinical hematologist, has been the involvement in diagnostic procedures that is so uncommon in most other specialities) we have to be realistic. Also, besides the technical developments that have taken place, clinical hematologists are under such huge pressure in their working environment that they are forced to push morphological examination to the edge of the agenda, and there is a tendency to concentrate hematologic diagnostics in big centers, often commercial facilities. These are all additional factors to take into consideration.

To put the question in another way, can morphology offer any answers that other techniques cannot provide?

First of all, the technique is quick and cheap, which makes it highly suitable for getting a first impression about what is behind an abnormality found at physical examination or in the blood cell count. Secondly, it can direct further diagnostic interventions if needed. Also, when further examinations are required, it can be used as a quality control: for example, are the cells of interest present in the sample, e.g. plasma cells when a myeloma is suspected or are there, in any case, enough cells for fluorescence *in situ* hybridization examination.

In the diagnosis and classification of hematologic malignant diseases, morphology is required by the WHO classification in the definition of blasts and monocytic lineage and in the description of myelodysplastic features.[9] In both cases, immunophenotype may help, but is not considered to be sufficient. However, several of the acute leukemias are no longer defined by blast count, and it is to be expected that this will apply to more of them when next-generation sequencing techniques have become a more common procedure in diagnostics. Also, definition of dysplasia by immunophenotypic, genetic or epigenetic changes may become more common. The same is true for the definition of complete remission in acute leukemias, currently defined by morphological blast count, but increasingly by immunophenotype and PCR-based techniques.

Taken together, and in spite of new developments, there remains a niche for morphological examination of the blood film or the bone marrow aspirate that is not easily replaced by other, more advanced techniques. This being the case, a second, more difficult, question arises. Does the clinical hematologist need to be involved in the morphological assessment? Frankly speaking the answer is "no". One example is those clinical oncologists who rely completely on the expertise of the pathologist for the diagnosis of the tumor. However, there are several arguments in favor of involving the clinical hematologist in the diagnostic process. The most important reason is the large diversity of the problems that may be hidden behind a putative minor abnormality, especially in the field of hematology. 'Leukopenia' can mean many things. A morphological examination will help ask the right questions to the right specialized laboratories or scientists who are used to starting with the destruction of the cells in order to make their own analysis. The final diagnosis and classification in hematologic malignancies is the product of the integration of many different results. Since, and not only according to the WHO classification, clinical data have to be included in this final classification, the clinical hematologist is the right person to combine the results from the different assessments and make an overall final conclusion. He is, after all, the person who initiated the diagnostic procedure and he is the one who can guide this process. And to do this efficiently and cost effectively, he may be the most suitable person to carry out the morphological screening.

The landscape of diagnostics in malignant hematology is changing towards a more high-tech approach and greater spe-

cialization, and the significance of morphology as part of this process is changing with it. So, what are the clinical hematologists going to do with their microscopes: use them or sell them?

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Disease severity in chronic graft-*versus*-host disease: doctors' gut feeling *versus* biostatistics?

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Chronic graft-*versus*-host disease (GVHD) is a frequent and potentially life-threatening complication of allogeneic hematopoietic stem cell transplantation. An increase in transplants in older patients and the more frequent use of unrelated donors have led to greater numbers of patients with this painful complication. Recent advances have been made in understanding the pathophysiology of chronic GVHD as well as in establishing precise criteria for the diagnosis and classification of disease manifestations. These advances will, it is hoped, pave the way to improving both the prophylaxis and treatment of chronic GVHD. We recently reviewed current issues in chronic GVHD with Dr. Ritz and readers of Haematologica interested in this field can find detailed information in this article.[1]

In the past, chronic GVHD included any clinical manifestations of GVHD that occurred beyond 100 days after transplantation. This definition was clearly imprecise and became inadequate. In 2005 a group of experts met under the auspices of the National Institutes of Health (NIH), USA in a consensus meeting. The goals of this NIH consensus working group on the diagnosis and staging of GVHD were: (i) to establish criteria for diagnosis of the disease, emphasizing the distinction between acute and chronic GVHD; (ii) to define criteria for scoring the severity of clinical manifestations in affected organs; and (iii) to propose categories describing the overall severity of the disease and the indications for treatment.[2]

The NIH consensus conference recognized two main categories of GVHD, each with two subcategories. The broad category of acute GVHD includes classic acute GVHD (maculopapular erythematous rash, gastrointestinal symptoms, or cholestatic hepatitis). The broad category of chronic GVHD includes classic chronic GVHD, presenting with manifestations that can be ascribed only to chronic GVHD. Chronic GVHD also includes an overlap syndrome, which has diagnostic or distinctive manifestations of chronic GVHD together with features typical of acute GVHD.

Numerous prognostic indices in chronic GVHD have been described.[1] Thrombocytopenia (platelet count $<100x10^9$/L) is the first reported and most reproducible prognostic factor even when using NIH criteria. Other factors, such as diarrhea, might be prognostic only due to the older definition of the disease or to the worse prognosis of the overlap syndrome. The NIH consensus conference proposed a new global chronic severity score establishing mild, moderate and severe forms of chronic GVHD based on a numerical scoring system for individual organs to calculate a summary scale.[2] Although the NIH global score was developed through expert opinion, several studies have shown that the global score at onset of chronic GVHD is associated with risk of subsequent mortality.[3-6] However as nicely described by Inamoto *et al*. in this issue of Haematologica,[7] several issues remain to be elucidated. Firstly, since the NIH global score was based on expert opinion and was not originally intended to predict mortality, does this score provide an optimal model for predicting mortality risk in patients with chronic GVHD? The authors hypothesized that empirically derived estimates of overall mortality risk incorporating the relative importance of different organ involvement might be more accurate