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A European consensus report on blood cell identification: terminology utilized and morphological diagnosis concordance among 28 experts from 17 countries within the European LeukemiaNet network WP10, on behalf of the ELN Morphology Faculty.

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For Peer Review

Introduction

Morphological evaluation of peripheral blood (PB) and bone marrow (BM) cells through microscopic examination of properly stained smears remains crucial in hematological diagnosis.

Many factors, such as differences in bone marrow processing procedures, staining, degree of skill in interpretation and terminology used, contribute to a lack of standardization of this diagnostic tool.

However, the new WHO classification highlights the importance of morphological aspects, quantitative as well as qualitative, for the recognition of disease entities and better stratification of patients with hematological neoplasms, particularly myeloid neoplasms and above all myelodysplastic syndromes (MDS). Evaluation of blood and bone marrow cytology is, together with bone marrow biopsy morphology, immunophenotyping and cytogenetics, a very important step in the integrated diagnostic process of hematological diseases.

The current information and communication technology (ICT) era provides the opportunity to exchange, via internet, images and information without geographic limitation, saving time and resources. In the field of hematology, many studies highlight the robustness of ICT for diagnostic assessment of blood cells¹⁻⁴. ICT is therefore well suited to pursue a full consensus in the assessment of cell morphology.

The European LeukemiaNet (ELN, www.leukemia-net.org) Network of Excellence is an EU project funded by the 6th Framework Programme and includes 162 participating centers in 33 countries, with more than 1000 researchers and associates. Its major goal is the construction of a cooperative network for improving leukemia diagnosis, care and research. The ELN Morphology Faculty (EMF), composed of 28 expert morphologists from 17 European countries, was organized as one of activities of the Diagnostic Platform (Work Package (WP10), focused on Flow Cytometric and Morphological diagnosis. The project started in February 2007 with the goal to increase quality of diagnostics based on cytomorphology as the first technique worldwide and to support this by a web based consensus report, including a uniform nomenclature.

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Design and Methods

This study was carried out in three consecutive steps, aimed to take advantage of individual competences, to train each other, and to reach a full consensus by the end of the study.

During all the phases of the study, all files containing cell names were analysed without knowledge of the identity of the faculty member from whom images originated.

Statistical analyses were performed with the MEDCALC statistical software (Mariakerke, Belgium).

First phase of the study

To test the methodology, 50 images with 139 consecutively numbered cells were provided by the chair of the EMF and uploaded onto a restricted web page in June 2007. A database containing name proposals (including alternative glossary options) for each labelled cell in terms of lineage and maturation stage, was sent to all EMF members. The initial lineage/morphological categories were: erythroid, granulocytic, lymphoid, megakaryocytic, monocytic, blast and "other". Monocytes were included into separate category, since atypical cells of the monocytic series still remain the most difficult to identify in PB and BM specimens both in health and disease⁵⁻⁷. Participating members were asked to indicate in the Excel file whether they agreed with proposed terminology or give an alternative definition for each labelled cell. After all answers had been collected, a preliminary version of a consensual ELN Blood Cells Glossary (EBCG) of morphological terms was created.

Each EMF member was then asked to provide at least 5 meaningful images of cells together with the proposed cell definition(s) in terms of lineage and maturation stage, with the possibility of a second option. It was specifically requested to use, when available, nomenclature from the preliminary version of the EBCG.

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3 At this phase, the Faculty was composed of 21 members and each cell definition was considered
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5 approved if agreement from at least 17 members was obtained, corresponding to a consensus of
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7 over 80%.
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10 11 *Delphi method*

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13 The Delphi technique⁸⁻¹⁰ is based on the Hegelian principle of achieving oneness of mind through
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15 a 3-step process of thesis, antithesis and synthesis. In thesis and antithesis all participants present
16
17 their opinion on a given subject and views and opposing views are established. In practice, it is a
18
19 structured process based on the collection of knowledge from a group of experts and rounds of
20
21 examination of proposals/questionnaires until consensus is obtained. The methodology has been
22
23 previously applied in several clinical studies, including attempts to obtain consensus in
24
25 histopathology¹¹. Delphi methodology was applied to the next step of our study to obtain better
26
27 consensus for cells without a full agreement (<17/21) during the first round of answers. As a pre-
28
29 requisite, one alternative term had to have been proposed by at least 3 members to be included
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31 into the options of the Delphi questionnaire. Moreover, cells with a full agreement ($\geq 17/21$) but with
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33 a different classification provided by at least 3/21 members were also submitted to the Delphi
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35 questionnaire, in order to discuss as many different options as possible.
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39 For this phase of the study, a new database was prepared, in which all cells without full agreement
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41 were listed with the proposed two or three options for terminology. For each option, the rate of
42
43 initial agreement was indicated as the number of faculty members in agreement. It was then
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45 proposed to score each option between 3 and 1, with 3 = full agreement, 2 = partial agreement, 1 =
46
47 full disagreement. Score 3 could be used only for one single option for each cell.
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51 Data were then summarized and a new Delphi round was performed for those cells presenting with
52
53 a low final score (<7) resulting from at least 2 full agreements.
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56 57 *Second phase of the study*

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59 In June 2008, the Faculty was extended to 28 morphologists with the aim to achieve a broader
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representation of countries taking part in ELN. In this phase of the study, each member submitted

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3 a set of two new images without providing cell names. Participants were asked to name each of
4
5 the submitted cells using cell definitions from the EBCG, whenever possible. The aim of this phase
6
7 was to evaluate the level of consensus reached by the EMF after the first training round of the
8
9 study. All data were collected, grouped and analysed with the same requirement of at least 80%
10
11 agreement for definite term used for a given cell.
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16 *Third phase of the study*

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18 In October 2008 during a two-day meeting in Nancy, we collectively reviewed i) the set of 79 cells
19
20 with a scoring difference <7 between two options after the first Delphi round and ii) the set of 98
21
22 not fully agreed cells submitted in the second phase without providing any cell name. Aims of this
23
24 phase of the study were to reach the highest possible consensus before uploading images onto the
25
26 ELN web site, to discuss and possibly find a consensus on all the problems faced during the
27
28 process, and to finally agree on the ELN Cell Glossary.
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33 **Results**

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38 One-hundred and sixty-four images containing 438 labelled blood cells were initially collected from
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40 the EMF members with the submitter's proposal(s) of term(s) for each labelled cell. The cell-
41
42 lineage distribution, according to the submitter's proposal was: granulocytic series 126 (29%),
43
44 erythroid series 77 (17.5%), monocytic series 35 (8%), lymphoid series 107 (24.5%),
45
46 megakaryocytic series 23 (5.5%), blasts 29 (6.5%) and "other" 41 (9.5%). During this primary
47
48 evaluation, a full consensus ($\geq 17/21$) was achieved for 250 cells (59.4%). The preliminary version
49
50 of the EBCG was prepared. Major discrepancies in morphological consensus concerned the
51
52 groups of blasts and monocytic series (Table 1). Another important discrepancy was due to
53
54 difference between the EBCG and the Anglo-American hematology experts concerning the terms
55
56 used to identify the differentiation stages of the erythroid series. In order to harmonize the EBCG,
57
58 we decided to add whenever necessary the alternative denomination in brackets, i.e. "erythroblast
59
60 basophilic (early erythroblast)".

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3 The first Delphi questionnaire was applied to a total of 216 cells, including 178 with <17/21
4 agreement and 38 cells with the same alternative classification provided by at least 3/21 members.
5
6 After discussion and review of the pictures, the EMF created a new category, "Cell to delete", for a
7 set of 8 cells, since disagreement or, more precisely, failure to reach a firm decision, was mostly
8 due to the poor quality of the images. Table 2 shows the subgroup partition of submitted cells
9 before and after the Delphi round. After the Delphi round the full agreement (lineage, cell
10 differentiation level, normal vs dysplastic feature) was reached on all of the 216 submitted cells and
11 the list of EBCG could be implemented.
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20 Seventy-nine cells, showing a scoring difference <7 between two options (resulting from two full
21 agreements or three partial agreements) were listed to be discussed during the consensus
22 meeting. Disagreement involved two major aspects: semantic problems and cell identification.
23
24 Many of the semantic problems were solved before the meeting, exchanging comments via
25 internet and adopting the agreed EBCG. The discussion of additional issues, such as limitation of
26 microscopic evaluation alone to define a lymphocyte as atypical or reactive, was further carried on
27 at the consensus meeting. One of the semantic concerns involved the term which had to be used
28 to identify a "morphologically abnormal" plasma cell: atypical or dysplastic. Another question which
29 had to be discussed collectively was if the term "dysplastic" should be used only for the three
30 myeloid lineages (granulocytic, erythroid, megakaryocytic) or not.
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42 With regard to cell identification, the majority of discrepancies concerned the decision if cells
43 should be considered normal or dysplastic. That problem was found in 2 cells of the
44 megakaryocytic series, 8 cells of the erythroid series and 24 cells of the granulocytic series.
45
46
47

48 Disagreement concerning a differentiation stage of a given cell was found for 3 cells of the
49 granulocytic series, 3 cells of the monocytic series and 1 cell of the erythroid series. For ten cells
50 disagreement concerned whether they should be identified as blast versus monoblast (5 cells),
51 promonocyte (4 cells) and promyelocyte (1 cell) (Table 3).
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57 In the second phase of the study, 64 new images with 162 labelled cells were collected: cells were
58 re-labelled from number 439 to 600 to follow the sequence of the previous set and uploaded onto
59 the restricted web page without any cell name proposal: EMF participants were asked to name the
60

1
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3 labelled cells, including their own, using the EBCG when possible. According to the cell name
4
5 provided by the submitters, the initial distribution of these 162 cells showed an increase in
6
7 monocytes and an equivalent decrease in granulocytes compared to the proportions of the first set
8
9 of 438 cells. Full agreement, including use of the same denomination, was reached immediately for
10
11 60 cells (36.14%). This was considered an important achievement, especially in the view of the
12
13 heterogeneity of the glossaries used in practice in hematology laboratories all over Europe. It
14
15 should be underlined that in this phase of the study, cells were submitted without a name proposal,
16
17 as for the first phase of this study. The remaining 102 cells were collectively discussed, agreed
18
19 upon and named during the two-day meeting (Table 4). Three additional cells were deleted, due to
20
21 the poor quality of the images. During the interactive discussion on the images, the EMF decided
22
23 to label 4 more cells because of their relevance in the context (1 blast NOC, 1 promyelocyte, 1
24
25 promonocyte and 1 megakaryoblast, respectively) and to add the category "Cytologically
26
27 unclassifiable" for 5 images displaying metastatic cells, previously included in the category "other".
28
29 The ECBG was updated.

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33 Major discrepancies on this set of cells concerned the appropriate use of terms such as dysplasia,
34
35 atypical or Mott cell. All the problems faced and all the points discussed were listed: a Consensus
36
37 statement document was approved: all the points are highlighted in the Discussion section. At the
38
39 end of the meeting 228 images with 604 labelled blood cells were available to be uploaded onto
40
41 the European LeukemiaNet website <http://www.leukemia-net.org> under the section Diagnostic
42
43 WP10, together with an Excel file (ECBG) where each cell is identified by its code, the type of stain
44
45 used, the lineage and the consensus name agreed by the EMF. All this material is currently freely
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47 available on the ELN web site and is linked to the EHA web site (<http://ehaweb.org>) under the
48
49 section >Education/distance training/ morphology database<.

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53 The EMF decided to highlight the cells agreed after the Delphi round and/or the meeting in Nancy,
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55 with a round red circle around the ID number, to point out all the problems discussed during this
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57 project.

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60 A set of 239 cells without the ID agreed by the Faculty, was submitted via internet to a recognized
expert morphologist (JMB) external to the EFM: after the first round, he rejected 34 cells as not

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3 well focused and identified 205, cells with a full agreement on 96 cells (46%) with the EFM
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5 identification. Details on cell distribution and agreements after the first round are reported in Table
6
7 5, including a subgroups of cells defined as dysplastic. In December 2009, during a meeting
8
9 focused on re-examining disagreements, only 7 cells were confirmed as disagreed and a final
10
11 agreement was reached on 205 valuable cells (96.6%). Main additional suggestions concern the
12
13 nomenclature of “immature monocyte” instead of “dysplastic monocyte”⁷ and a better definition of
14
15 the term “dysplastic promyelocyte”¹². The quite full concordance achieved after the second
16
17 interactive reviewing process support the realistic need in the field of cytomorphology to share
18
19 consensus, including nomenclature, to increase quality of diagnostics according to WHO 2008
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21 goals and guidelines.
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27 **Discussion and consensus statement**

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29 This manuscript describes the methodology used to develop a consensual glossary for the
30
31 denomination of hematopoietic cells within the European LeukemiaNet “diagnostics” workpackage.
32
33 This highly interactive work was made possible through the use of modern communication means,
34
35 and required only one two-day meeting of actual confrontation and debate. It resulted in the
36
37 production of a freely accessible tool that could be useful for training as well as harmonization of
38
39 morphological reports in oncohematology especially, without geographic limitation (i.e., not limited
40
41 to European countries).
42

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44 Significant omissions in the archive should be identified in the future and contributions should be
45
46 sought for inclusion after validation.
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49 Moreover, this collective work resulted in the production of a consensus statement as summarized
50
51 below, taking into account individual practices, collegial agreement and literature data.
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55 1- In building a photographic archive it is essential to use well stained films and to select cells in a
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57 part of the film that is not too thick. Precise focus and a high enough power to clearly assess
58
59 cellular details are essential. The stain used should be specified only if it was not a May–
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Grünwald–Giemsa or similar Romanowsky-type stain. The magnification should not be stated

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3 since this becomes irrelevant when cells are viewed at varying magnifications by users of the
4
5 archive and since there is almost invariably an erythrocyte present that can provide a basis for
6
7 comparison.
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10 2- When significant extra information that makes the photograph more informative is available, this
11
12 should be added. When brief information is sufficient it should be provided in brackets, e.g.
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14 erythroblast, vacuolated (alcohol excess).
15

16
17 3- Erythroid precursors can be designated by two parallel sets of names, as customarily used in
18
19 different countries: Proerythroblast, Basophilic erythroblast or early erythroblast, Polychromatic
20
21 erythroblast or intermediate erythroblast, Orthochromatic erythroblast or late erythroblast-
22

23
24 4- Megaloblasts can be designated in an equivalent manner: Promegaloblast, Early, Intermediate
25
26 and Late megaloblast.

27
28 5- A neutrophil should be regarded as hypersegmented only when it has a minimum of 6 lobes.

29
30 Assessment of hypersegmentation on the basis of an increased proportion of 5-lobed neutrophils
31
32 cannot be based on a single cell.

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34 6- Dysplasia is a description of morphologically abnormal development and is not synonymous with
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36 myelodysplastic syndromes (MDS).
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39 7- The term 'dysplastic' should only be used for the three myeloid lineages. For cells of other
40
41 lineages showing similar morphologically abnormal development, e.g. lymphocytes and plasma
42
43 cells the convention of using the term 'atypical' should be followed. Despite their myeloid nature,
44
45 the convention of applying 'atypical' also to mast cells is supported.
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48 8- Dysplastic hemopoiesis can lead to the production of cytologically abnormal erythrocytes (e.g.
49
50 poikilocytes or a dimorphic population) or platelets (e.g. giant, hypogranular or with abnormal
51
52 granules); however the term 'dysplasia' should be confined to nucleated cells.

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54 9- It was emphasized that dysplasia should not be assessed in patients receiving growth factors
55
56 and, furthermore, that, since heavy neutrophil granulation is often the result of sepsis, its presence
57
58 should not be included in the quantification of dysplastic features for the diagnosis of MDS or for
59
60 the recognition of multilineage dysplasia in AML.

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3 10- In scoring the percentage of dysplastic cells for the purpose of diagnosis and classification,
4 subtle abnormalities should not be considered sufficient to categorize a cell as dysplastic, like in
5 the WHO classification.
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10 11- The abnormal cells of acute promyelocytic leukaemia should be designated like in the WHO
11 classification as hypergranular and microgranular (hypogranular) promyelocytes respectively.
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13 Although both forms are dysplastic, the word 'dysplastic' is not needed in the designation.
14

15 Hypogranular promyelocytes of other types should be included in the general category of
16 'dysplastic promyelocyte'.
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19
20 12- The blast definition proposed by the International Working Group on Morphology of MDS ¹²
21 should be used. Briefly, this designation recognizes agranular and granular blast cells with the
22 latter differing from type II blast cells as defined by the French–American–British (FAB) group in
23 that they may have more than 'scanty' granules but have all the other characteristics of blast cells.
24
25 Blast cells that cannot be recognised as belonging to a specific lineage should be designated
26 'blast, not otherwise categorized'. Assigning lineage to blast cells is facilitated by assessing cells in
27 relation to each other rather than in isolation.
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30
31 13- Monoblasts and promonocytes should be defined as in the WHO classification ⁶. A monoblast
32 has a round or oval nucleus. A promonocyte has a convoluted, folded or grooved nucleus. In the
33 WHO classification, a promonocyte is a blast equivalent and the term should therefore be applied
34 only to a cell that has a delicate or dispersed chromatin pattern, equivalent to that of a monoblast.
35
36 Distinction between a monoblast and a promonocyte is not of practical importance since they are
37 regarded as having the same significance. However, distinction between a promonocyte and an
38 atypical/abnormal/immature monocyte can be very difficult. A lack of rigour in applying the defining
39 criteria of promonocyte definition may lead to monocytes being misclassified as promonocytes,
40 which could in turn lead to an erroneous assessment of the number of blasts plus blast equivalents
41 and thus to a misdiagnosis of chronic myelomonocytic leukaemia as acute monocytic leukaemia.
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43 Appreciation of the immature chromatin pattern is crucial in recognition of a cell of monocyte
44 lineage as a blast equivalent.
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3 14- Based on morphology alone, atypical lymphocytes should be further divided into i) Atypical
4 lymphocyte, suspect reactive ii) Atypical lymphocyte, suspect neoplastic iii) Atypical lymphocyte,
5 uncertain nature.
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10 15- In general it is preferable to avoid the use of eponymous names to identify cells or peculiar
11 morphological patterns. However some names are well established and have a clear meaning (e.g.
12 Auer rods) and their use should continue.
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16 16- 'Mott cell' and 'Russell bodies' are used differently in different European countries. The original
17 papers of Mott, Russell and also Dutcher were therefore reviewed after the meeting. Dutcher
18 bodies, single or multiple Russell bodies and the inclusions of Mott cells¹³⁻¹⁸ are the morphological
19 evidence of the same cytoplasmic inclusion(s), in the case of Dutcher bodies being invaginated
20 into the nucleus. Mott cells contain Russell bodies. The proposed term to identify plasma cells with
21 this morphological pattern is: plasma cell, atypical, with nuclear inclusions or plasma cell, atypical,
22 with cytoplasmic inclusions/vacuoles.
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32 17- The term 'macrophage' should be used for a potentially phagocytic cell derived from a
33 monocyte. The term 'histiocyte' has a broader use, including macrophages and dendritic cells such
34 as Langerhans cells, not normally seen on PB or BM smears.
35
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38 18- When examining a single cell, cytological criteria do not permit a distinction between Gaucher
39 cells and pseudo-Gaucher cells and both should therefore be categorised as 'Gaucher cells' with
40 an explanation between quotes, e.g. 'Gaucher disease' or 'pseudo-Gaucher cell' in chronic myeloid
41 leukaemia'.
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47 19- In general bone marrow aspirates are not appropriate for the diagnosis of cancer. However,
48 collections of immature cells in a syncytial cluster is suggestive of metastatic cancer and should
49 be reported as 'Cytologically unclassifiable' and should be confirmed with a bone marrow biopsy
50 and appropriate immunostains.
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56
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60**Table 1**

First phase: cell lineage distribution according to initial submitters' proposals, EMF Full agreement and EMF Not-full agreement.

Cell series	Initial proposal of 438 submitted cells n= (%)	Agreement $\geq 17/21$ on 260 cells (59.4% of submitted cells) n=	Agreement $< 17/21$ on 178 cells (40.6% of submitted cells) n=
Granulocytic	126 (29%)	75	51
Erythroid	77 (17.5%)	53	24
Monocytic	35 (8%)	12	23
Lymphoid	107 (24.5%)	64	43
Blast	29 (6.5%)	6	23
Megakaryocytic	23 (5%)	16	7
Other	41 (9.5%)	34	7

Table 2.Distribution of 216* cells **Before** and **After** Delphi round.

#216 cells (49,3% out of 438 submitted cells)	Cell distribution Before the Delphi round n= (%)	Cell distribution After the Delphi round n= (%)
Granulocytic series	65 (30%)	61 (28%)
Erythroid series	28 (13%)	27 (12.5%)
Monocytic series	24 (11%)	24 (11%)
Lymphoid series	52 (24%)	48 (22%)
Blast	26 (12%)	30 (14%)
Megakaryocytic series	8 (4%)	6 (3%)
Other	13 (6%)	12 (5.5%)
To delete		8 (3%)

* This number includes 178 cells with an agreement < 17/21 plus n=37 cells with an agreement ≥17/21 associated with the same alternative proposal by 3 or 4 Faculty Members

Table 3.

Morphological cell-term options of 79 cells showing a scoring difference <7 between 2 options after the Delphi round (the first option is the quoted one).

Series/Subgroups	Cells	Cell-term options
Granulocytic (26)	promyelocyte (16)	dysplastic vs normal (7)
		dysplastic vs blast (1)
		abnormal vs blast (2)
		abnormal vs promyelocyte, abnormal, hypergranular (2)
		promyelocyte vs promyelocyte, hypergranular (2)
		promyelocyte vs to delete (1)
		promyelocyte vs myelocyte (1)
	myelocyte (1)	myelocyte, eosinophilic, dysplastic vs metamyelocyte, eosinophilic (1)
	metamyelocytes (2)	metamyelocyte, eosinophilic vs myelocyte, eosinophilic (1) metamyelocyte, dysplastic, pseudo-Pelger vs metamyelocyte, dysplastic (1)
	neutrophil (4)	dysplastic vs normal (3) dysplastic vs apoptotic (1)
	mast cell (3)	atypical vs normal (3)
Erythroid (9)	basophilic (1) polychromatic (6) orthochromatic (1) promegaloblast (1)	dysplastic vs normal (8)
		promegaloblast vs erythroblast basophilic (early) megaloblastic (1)
		monoblast vs blast (3)
		promonocyte vs blast (2)
Monocytic (12)	monoblast promonocyte	promonocyte vs monocyte dyspl. (1)
		promonocyte dysplastic vs monocyte dysplastic (1)
		monocyte, early vs promonocyte (3)
		dysplastic vs normal (1)
		dysplastic vs to delete (1)
	monocyte, early monocyte	
Lymphoid (16)	lymphocyte (5)	lymphocyte vs lymph, villous (1)
		cleaved vs prolymphocyte (1)
		atypical vs to delete (2)
		LGL vs to delete (1)
		dysplastic vs atypical (9)
		atypical vs plasmablast (1)
	plasma cells (11)	atypical vs to delete (1)
Blast (6)	blast (6)	blast vs monoblast (2)
		blast vs promonocyte (2)
		blast vs promyelocyte (1)
		blast vs blast, peroxidase negative (1)
Megakaryocytic (3)	Megakaryocyte (2) megakaryoblast (1)	dysplastic vs normal (2)
		megakaryoblast vs micromegakaryoblast (1)
Other (1)	histiocyte (1)	histiocyte, malignant histiocytosis vs histiocyte, immature
To delete (6)	to delete	to delete vs: smear cell (1), blast (3), plasma cell immature (1), erythroblast dysplastic (1), mast cell (1)

Table 4

The second phase of study: Distribution of the submitted cell lineage before and after the discussion at the meeting in Nancy.

Cell distribution	Cell distribution <i>Before</i> the meeting in Nancy (162 submitted cells)	Cell distribution <i>After</i> the meeting in Nancy (162 plus 4 added cells)
Granulocytic series	38 (23.5%)	39 (23.5%)
Erythroid series	30 (18.5%)	31 (19%)
Monocytic series	20 (12%)	17 (10%)
Lymphoid series	42 (26%)	35 (21%)
Blast	8 (5%)	
Blast NOC*		14 (8,5%)
Megakaryocytic series	11 (7%)	15 (9%)
Other	13 (8%)	7 (4%)
To delete		3 (2%)
Cytologically unclassifiable		5 (3%)

* NOC: Not Otherwise Categorized

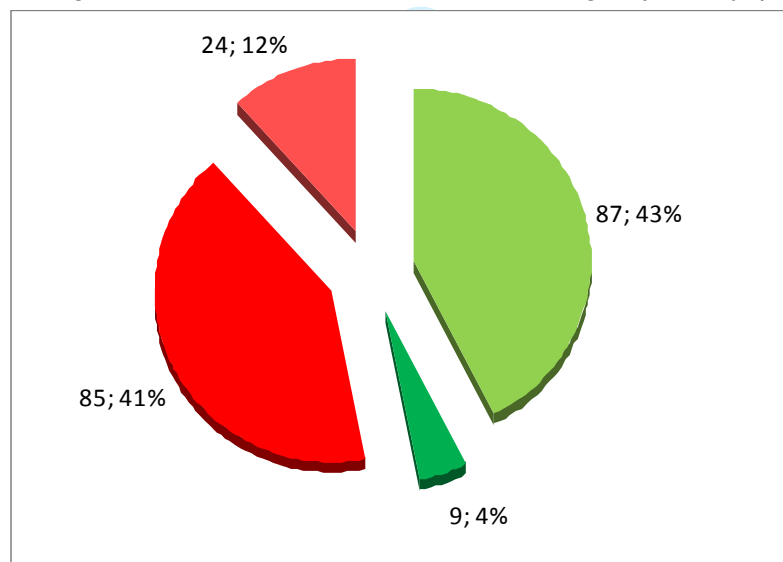
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Table 5.

5a. Distribution of 205 cells submitted to an expert morphologist external to the EFM.

Evaluable cells	205
Cytologically unclassifiable	5
Erythroid series	40
Granulocytic series	59
Lymphoid series	40
Megakaryocytic series	16
Monocytic series	19
NOC (not otherwise categorized)	13
Not evaluable	4
Other	9

5b. Agreement after a first round via net: subgroups of dysplastic cells are highlighted-



1	87	agreed cells
2	9	agreed dysplastic cells
3	85	disagreed cells
4	24	disagreed cells dysplasia yes/no