The differential diagnosis between aplastic anemia and hypocellular myelodysplasia in patients with pancytopenia

Sir,

The differential diagnosis between hypocellular myelodysplasia (h-MDS) and aplastic anemia (AA) may be diffucult.[1-5] In the present study we looked for new parameters that could be used for this purpose.

Adult patients with pancytopenia and hypocellular bone marrow were studied. The criteria for h-MDS were: >5% of blasts in BM smears, ALIPs in BM sections, clonal cytogenetic abnormality or at least two of the following parameters: 1. blasts in the peripheral blood; 2. ring sideroblasts; 3. atypical granulocytic precursors or megakaryocytes. BM sections were analyzed for number of factor VIII positive cells. Cellularity was classified as: 1. pronounced hypocellularity; 2. highly variable cellularity ranging from normocellular areas to markedly hypocellular ones; 3. moderately decreased hemopoiesis.

Significant ($p<0.05$) parameters were included in a stepwise linear discriminant analysis (LDA) (criterium: minimization of Wilk's λ) followed by a *jackknife* procedure.[6,7] An index was created by summing the mean standardized coefficients divided by the means of the variables (categorical variables: 0/+1). The *cut-off-range* was defined as the 99%-CI of the cut-points, obtained by LDA of 150 bootstrap samples (with replacement).

In h-MDS atypical neutrophils and blasts were not observed in peripheral blood. In BM, megakaryocytes were atypical in 71% (Table 1). ALIPs were found in 11/29. An irregular distribution of hemopoiesis was seen in 51.7%, accompanied by clustering of megakaryocytes (Figure 1). Cytogenetic analysis gave mitoses in 20% of the samples (one trisomy 8, 7 normal karyotypes).

In AA, cell atypias was found only in erythroblasts. Megakaryocytes were seen in only one case. In 24/30 cases hemopoiesis was markedly decreased in BM sections.

Discriminant analysis was performed with the peripheral blood and BM histologic parameters which were available for all cases. The final model (Wilk's $\lambda = 0.367$; $p<0.0001$) contained *age*, *percentage of circulating neutrophils; marked BM hypocellularity* and *presence of megakaryocytes* and correctly classified in 89.8% (before and after the *jackknife* procedure)

The diagnostic index was defined as I = 0.01 x age + 0.01 x percentage of neutrophils + 0.85 x presence of megakaryocytes – 1.58 x marked BM cellularity; (cut-off between 0.40 and 0.80). Values < 0.40 favored the diagnosis of AA and those > 0.80 that of h-MDS. Applied to our initial data 86% of cases were correctly classified.

A significant proportion of patients with MDS have a hypocellular marrow, and this proportion increas-

Table 1. Clinical and hematologic data of the patients. (95% confidence intervals in brackets).

Variables	*AA*	*MDS*	*p value*
Number of cases	30	29	
Age (years)	28 (11.8-57.9)	41 (14.0-79.8)	0.005
Hemoglobin g%	7.9 (2.8-12.1)	9.3 (5.4-12.4)	0.110
Leukocytes x 10^9/L	2.8 (0.86-4.89)	3.2 (0.90-4.95)	0.572
Neutrophils %	27.6 (5.1-62.5)	42.3 (7.5-75.0)	0.003
Lymphocytes %	67 (27.8-90.9)	51 (21.5-86.5)	0,004
Monocytes %	3.5 (0.0-10.0)	3.4 (0.15-14.0)	0.730
Platelets x 10^9/L	31.5 (1.6-60.5)	54.0 (3.0-100.0)	0.037
BM cytology*			
Erythroblasts %	20.0 (3.0-59.3)	25.7 (2.8-57.0)	0.13
Granulocytes %	19.9 (1.7-58.5)	39.6 (15.4-78.0)	<0.001
Blasts > 5%	0/26	3/24	0.48
Lymphocytes %	52.5 (9.4-91.1)	27.9 (5.3-63.0)	0.003
Atypical erythroblasts	12/26	17/24	0.246
BM cellularity (sections)			
Markedly decreased	24	4	< 0.0001
Irregular distribution	5	15	
Moderately decreased	1	10	
Absence of megakaryocytes	21/30	1/29	<0.0001
Mean number°	0.13 (0-1.0)	4.0 (0-26.1)	<0.0001
Increased reticulin fibers	3	6	0.36

**Based on 50 cases with a representative smear; °counted in sections immunostained for factor VIII (10 high power fields). Parameters were compared by the two-tailed Mann-Whitney's or the Fisher exact test . Correction of Cross and Chaffin: p<0.0056 is significant. All continuous variables with exception of platelet counts had a Gaussian distribution.*

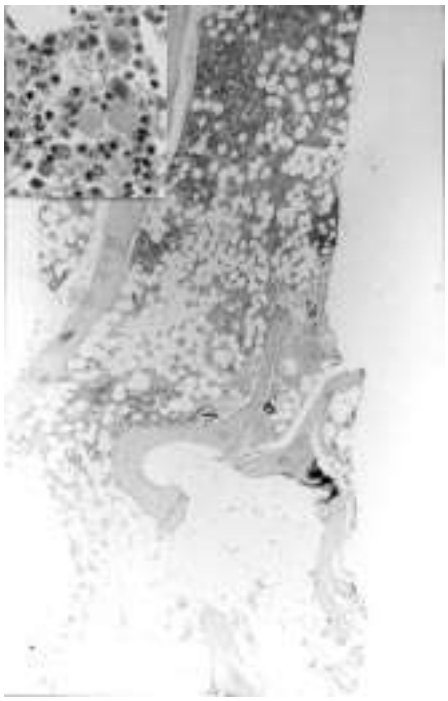

Figure 1. Bone marrow section of a patient with h-MDS, showing the transition between a cellular area and a markedly hypocellular one. Inset: high magnification of a cellular area with a cluster of megakaryocytes.

es in secondary cases.[2,8-10] h-MDS is considered a new entity, outside the FAB classification but related to refractory anemia.[1,2,4] Evolution to MDS has been observed during the follow-up of non-transplanted patients with AA. Since prognosis and treatment are different in both entities, differential diagnosis is important. As detection of clonality is not possible in many cases,[1,2,5] differentiation is based predominantly on morphologic parameters.

Half of our cases with h-MDS had an irregular distribution of hemopoiesis. Presence and morphology of megakaryocytes were more important criteria than features of erythroblasts and granulocytes. However, since no single new parameter enabled us to differentiate the two diagnostic groups clearly, a linear discriminant analysis was performed. Using an algorithm based on the combination of the four *new* parameters described, nearly 90% of the cases could be correctly classified. The *jackknife* procedure showed that the model was stable and we could create therefore an index which can be used easily in daily practice.

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Key words

Aplastic anemia, myelodysplasia, megakaryocytes, bone marrow histology, linear discriminant analysis

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Parotid and central nervous system relapse during complete hematological remission in acute promyelocytic leukemia

Sir,

Extramedullary leukemic infiltration is rarely observed in patients with acute promyelocytic leukemia (APL).[1] To our knowledge only 32 cases of extramedullary APL have been reported.[1-10] The extramedullary sites reported are skin, soft tissue, gingiva, breast, mandible, thymus, mediastinum, lymph node, spleen, liver, colon, optic nerve, external auditory canal and central nervous system (CNS). Some of these cases had extramedullary relapse with bone marrow in remission.[1] Some authors hypothesize that all-trans retinoic acid (ATRA) treatment for APL may be associated with an increased incidence of extramedullary disease at the time of relapse,[3,4,6-9] although a direct causal link has not been established, and this hypothesis lacks, at present, any statistical confirmation. The majority of the previously reported patients with extramedullary APL were treated only with standard cytotoxic chemotherapy.[1]

In June 1984, a 13-year-old girl presented with morphologically classic APL. A cytogenetic examination demonstrated 46XX, t(15; 17) in all 20 cells analyzed. After a month the patient gained complete remission (CR) with daunorubicin and received consolidation and maintenance chemotherapy with alternating cycles of POMP, TRAP and COAP. Her disease remained in hematologic and cytogenetic remission until August 1996, when she presented with headache and a left parotid tumor. Excisional biopsy of the parotid revealed extramedullary APL. Immunohistochemistry stains were negative for LCA, L26, VHCL-1 and HAM 56, and naphthol chloracetate esterase. Biopsy material was not useful for molecular or cytogenetic studies. CAT of the brain showed a high-density mass in the left cerebral hemi-