Acute Promyelocytic Leukaemia
— Microgranular Variant —

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SUMMARY

Eight cases of acute promyelocytic leukaemia were diagnosed in the Department of Pathology CWM Hospital during a two and a half year period from January 1983 to June 1985. All of these belonged to the subgroup of microgranular acute promyelocytic leukaemia. This sub classification was done, based on the peripheral smear and bone marrow. The main aim of presenting these cases is to highlight the morphologic features and the clinical presentation of this variant.

INTRODUCTION

Acute promyelocytic leukaemia (APL) classified as M^3 of the FAB classification is a unique form of leukaemia characterised by the replacement of the bone marrow by abnormal promyelocytes and bleeding tendency due to intravascular coagulation.

Recently, besides the classicial hypergranular form, another morphological variant, the microgranular or atypical acute promyelocytic leukaemia has been described. The two types are differentiated on the basis of the morphological characteristics of the predominant leukaemic promyeloctye.

With the exception of bleeding most of the clinical features of an acute leukaemia may be completely absent. Morphological appearances of abnormal cells seen in the peripheral smear raises ones suspicion. The conclusive diagnosis is made by bone marrow aspiration and cytochemical profile.

The purpose of this paper is to highlight the unusual clinical presentation and to describe the morphologic characteristics of microgranular promyelocytes.

MATERIALS AND METHOD:

Eight cases of acute promyelocytic leukaemia — microgranular variant were diagnosed in the Department of Pathology CWM Hospital. Bone Marrow and blood smears of seven patients were sent to Department of Haematology, Auckland Hospital for confirmation. Basic haematological tests such as haemoglobin, total and differential WBC count, platelet count, ESR, coagulation profile and peripheral smear examination were done.

Bone marrow was obtained and prepared for examination in all the cases. The marrow and peripheral smear were stained with Leishman's stain. Cytochemical profile using peroxidase stain was done on peripheral film and bone marrow smears.

CLINICAL PRESENTATION (Table I)

Four of the eight patients were males and four females. The age of the patients ranged from 7 years to 59 years. Six out of eight patients presented with some sort of bleeding in the form of haematemesis or malaena or epistaxis or ecchymosis or petechial haemorrhages. Three patients had retinal haemorrhage. Fever was seen in all patients and lymphadenopathy in two patients only. Splenomegaly was rare and seen in one patient, with hepatomegaly present in 4 patients (50%).

One patient (E) presented with signs and symptoms of meningeal leukaemia. She presented with signs of raised intracranial pressure, left facial palsy, decreased power (Grade IV) on the left side and urinary incontinence. One patient (G) presented to the dental clinic with gingivitis.

Table I
CLINICAL PRESENTATION

Symptom/Sign	Present study Total cases 8		McKenna and others Total cases 7	
Splenomegaly	1	(13%)	1/7	(14%)
Hepatomegaly	4	(50%)	0/7	
Lymphadenopathy	2	(25%)	1/6	(17%)
Bleeding	3	(38%)	4/7	(51%)
Ecchymoses	2	(25%)	3/7	(43%)
Petechiae	2	(25%)	2/7	(28%)
Gum hypertrophy	2	(25%)	—	—
Retinal haemorrhages	3	(38%)	—	—
Fever	8	(100%)	—	—

LABORATORY FINDINGS (Table II)

All the patients had moderate to severe anaemia at diagnosis. Total white cell counts varied from 11,100 to 114,000 cells/cmm. Seven of the eight patients had greater than 80% immature cells in the bone marrow. Severe thrombocytopenia was noted in all cases. The platelet count ranged from 10,000/cmm to 50,000/cmm.

CYTOCHEMISTRY

Cytochemical stains were done on all cases for myeloperoxidase both on the blood film and bone marrow. All the immature cells showed strong peroxidase activity

especially in the golgi area in the form of dark dense granules (Fig I). Esterase stain was negative in all the cases.

Table II
AGE, SEX AND HAEMATOLOGICAL DATA AT DIAGNOSIS

	A	B	C	D	E	F	G	H
Age (Years)	26	23	59	19	12	17	26	7
Sex	M	F	M	M	F	F	M	F
Hb (grm %)	9.0	2.1	7.1	4.2	9.8	6.4	6.1	4.2
Total WBC count (cells/cub mm)	114000	29300	102400	10800	12500	11100	51800	22600
Platelets (cells/cub mm)	20000	10000	40000	20000	50000	20000	20000	20000
Promyelocytes % Blood	75	70	90	20	30	41	41	37
Promyelocytes % Marrow	80	80	95	80	80	60	80	80
Survival (in days after diagnosis)	Patient returned to Tuvalu	74	9	73	86	57	2	Patient went to Canada for treatment

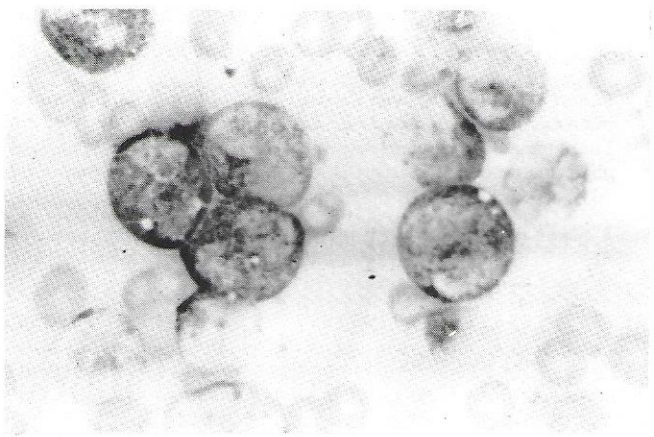

Fig. 1

MORPHOLOGY

The hypergranular promyelocytes are characterised by abnormal promyelocytes with a characteristic pattern of heavy granulation. The nucleus in this form greatly varies in size and shape being **reniform** or bilobed. The cytoplasm of most cells is completely occupied by large bright pink or red granules when stained with Romanowsky dyes. Cells characterised by bundles of Auer rods ("faggots") are invariably present in the bone marrow and blood film.

The atypical or microgranular variant showed a pleomorphic population of cells. There was relative scarcity of cells with heavy granulation or multiple Auer rods. The nucleus of most of the cells were bilobed multilobed or reniform, but the majority of cells were either devoid of granules or contained fine azurophilic granules (Fig 2). The chromatin was reticular with prominent nucleoli. In addition significant numbers of promyelocytes showed large abnormal vacuoles in the cytoplasm. (Fig 3). A good number of cells showed prominent golgi area.

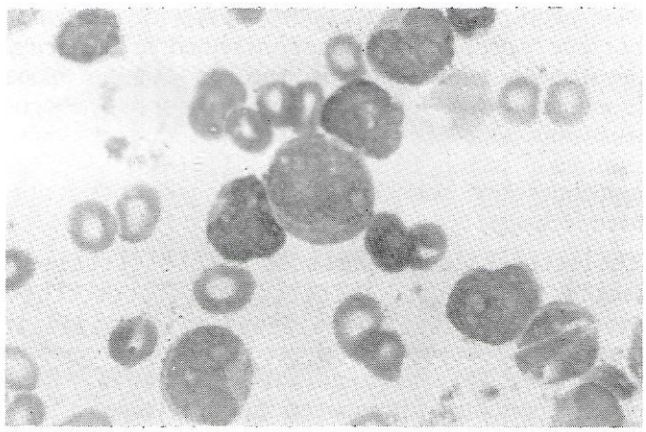

Fig. 2

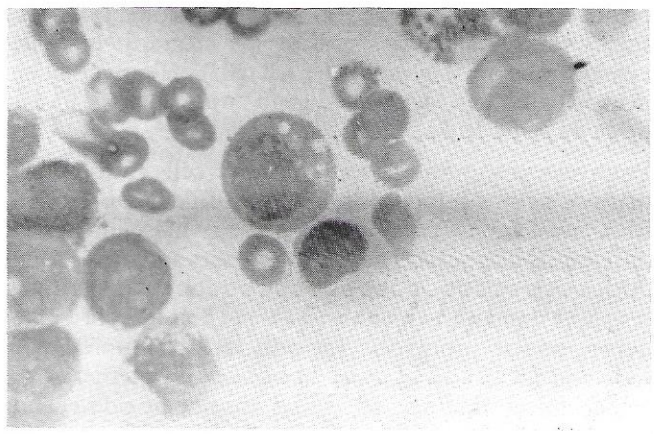

Fig. 3

TREATMENT AND SURVIVAL

All patients except one had symptomatic treatment. The survival was poor. One patient went to Canada for further treatment. It has been found that these patients have poor survival even with treatment. The main cause of death is disseminated intravascular coagulation.

DISCUSSION

Recently a morphologic variant of acute promyelocytic leukaemia (FAB classification M^3) has been described in which most of the leukaemic promyelocytes lack hypergranulation. Severe disseminated intravascular coagulation is seen in these patients.

Cases of microgranular acute promyelocytic leukaemia have to be distinguished from myelomonocytic leukaemia (FAB M^4) which is the most important differential diagnosis. The presence of some hypergranular promyelocytes, cells with multiple Auer rods and inclusions of Auer like material together with cytochemical findings of strong myeloperoxidase and weak or negative esterase in microgranular acute promyelocytic leukaemia distinguishes it from acute myelomonocytic leukaemia.

The prominent clinical features in the cases seen were anaemia and fever. Splenomegaly and lymphadenopathy were inconspicuous. Bleeding of some sort was noted in all but one patient. One patient presented to the dental department with gingivitis and on routine blood examination was found to have acute promyelocytic leukaemia. One patient presented with unusual clinical features of meningeal leukaemia. Three cases in which opthalmoscopy was done showed bilateral retinal haemorrhages.

The haematological parameters showed white cell counts ranging from normal to marked leucocytosis. Three patients showed white cells counts that were around normal while two patients showed marked leucocytosis. The average white cell count was 44,300/cumm. All the patients presented with marked thrombocytopenia.

The presence of a high percentage abnormal promyelocytes in the peripheral smear made one suspect acute leukaemia in all the cases. Two cases showed the presence of abnormal monocytoid cells in the peripheral smear which made one consider the diagnosis of acute myelomonocytic leukaemia (FAB M^4). However bone marrow findings were consistent with microgranular promyelocytic leukaemia.

Promyelocytes outnumbered all other cells in the bone marrow with a minimum of 60% recorded. Distinction from myelomonocytic leukaemia is the most important differential diagnosis. The sparse granules and the striking nuclear irregularity of microgranular promyelocytes may resemble immature monocytes. The presence of some hypergranular promyelocytes cells with multiple Auer rods and inclusions of Auer like material together with cytochemical findings of strong myeloperoxidase and weak or negative non specific esterase in microgranular acute promyelocytic leukaemia should eliminate the confusion with acute myelomonocytic leukaemia.

The prognosis of these patients even with treatment is poor. In a series by Nand Kumar and others (1983) of eight patients put on regime normally employed for acute myeloid leukaemia viz thioguanine, cytosinearabinoside and daunomycin — six did not attain remissions and died within three months. Six of the patients at CWM Hospital who had symptomatic treatment only had an average survival of 50 days.

In order to make a diagnosis of microgranular acute promyelocytic leukaemia certain important morphological features have to be looked for. The presence of some hypergranular promyelocytes, cells with Auer rods and Auer like material, the presence of hyperbasophilic promyelocytes, the presence of folded, lobulated or reniform nuclei and cytochemical findings of strong myeloperoxidase helps one to make a diagnosis of microgranular acute promyelocytic leukaemia.

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