Myelodysplasia

Peter Jacobs, MB BCh, MD, PhD (Med), DSc (Med Sci), FRCP (Edin), MACP, FCP (SA), FRCPath (UK), IFCAP, MASSAf, FRSSAf

Emeritus Professor of Haematology, University of Cape Town, Honorary Consultant Physician, Groote Schuur Hospital Teaching Group, Professor of Internal Medicine, College of Medicine, University of Nebraska Medical Centre, Professor Extraordinaire in Haematological Pathology, Stellenbosch University and Tygerberg Academic Hospital, and Haematology Research Group, PathCare

Lucille Wood, FRCP (Edin), BA (Nursing Science), MSc (Med) (Haematol), RN,RM, Diploma in Intensive Nursing Care, Ward Administration and Clinical Teaching

Medical Biological Scientist, Senior Lecturer Extraordinaire in Clinical Haematology, Stellenbosch University and Tygerberg Academic Hospital, and Haematology Research Group, PathCare

Correspondence to: Natasha Gordon (natasha.gordon@pathcare.co.za)

This is the second in our series of clinical articles that discuss everyday presentations. Each emphasises practical aspects of team-based care that are relevant for general practitioners, specialists and paramedical professionals. Disorders arising in blood and bone marrow result in some of the commonest presenting symptoms and signs. A careful history and physical examination, complemented by rational use of laboratory tests, provides the clinical basis for a working diagnosis. If further investigation is needed into bone marrow or plasma, then supplementary imaging and radionuclide technology may be necessary under the guidance of an experienced haematologist.

These clinical syndromes occur commonly in everyday practice and have variable and often subtle manifestations. The myelodysplasias are a heterogeneous group of malignant stem cell disorders that differ widely in haematological presentation and natural history. The characteristic features are:
- cytomorphological dysplasia
- hypercellular bone marrow in the face of pancytopenia, reflecting ineffective blood cell production
- a variable risk of transformation to acute leukaemia.

These neoplasms may arise *de novo* or after exposure to potentially mutagenic therapy. They are more common in older adults, but are increasingly recognised in children or young adults. Affected individuals are often underdiagnosed and may be treated inappropriately or unnecessarily. This is avoidable given current, and improving, understanding of these fluid-phase tumours.

Background

More than 50 years ago cases of anaemia that did not respond to available therapy were recognised, of which about two-thirds defied diagnosis. Shortly thereafter some cases of refractory cytopenia were noted to develop into leukaemia, giving rise to the term pre-leukaemia. It was, however, not until 1970 that a classification was attempted, which was refined in 1976 by European, American and British investigators (Table 1).[1]

Table 1. French-American-British Co-operative Group Classification

Type	Percentage blasts		Monocytes 1x10⁹/l	Ringed sideroblasts
	Bone marrow	Peripheral blood		
Refractory anaemia (RA)	<5	≤1	-	-
Refractory anaemia with ringed sideroblasts (RARS)	<5	≤1	-	+
Refractory anaemia with excess blasts (RAEB)	5 - 20	<5	-	±
Chronic myelomonocytic leukaemia (CMML)	≤20	<5	+	±
RAEB in transformation (RAEB-T)	21 - 30	≥5	±	±

Bennett, *et al.*[1]

This was the initial approach to providing unification of these heterogeneous stem cell disorders. Ringed sideroblasts exceeding 15% of nucleated erythroid series classically in RARS but variably present in CMML and RAEB.

Table 2. World Health Organization Classification, 2008

Clinical presentation	Cytogenetic abnormalities (%)	Marrow blasts (%)	Disease
Anaemia – isolated	25	<5	RA
≥15% ringed sideroblasts	5 - 20	<5	RARS – with ring sideroblasts
Anaemia – normal platelets	100	<5	5q-syndrome
Bicytopenia or pancytopenia ±15 ring sideroblasts	50	<5	Refractory cytopenia with multilineage dysplasia (RCMD)
Cytopenias Blood blasts <5%	30 - 50	5 - 9	Refractory anaemia with excess blasts (RAEB1)
Cytopenias, peripheral blood blasts present	50 - 70	10 - 19	Refractory anaemia with excess blasts (RAEB2)
Neutropenia or thrombocytopenia	50	<5	Myelodysplastic syndrome, unclassified

Swerdlow, et al.[2]

Initially in 2001 the World Health Organization proposed an update that largely replaced the earlier classification. This has undergone extensive review and represents a worldwide consensus for approaching haematological neoplasms.

Table 3. International prognostic scoring system

Criteria	Score value				
Prognostic risk factor	0	0.5	1	1.5	2
Bone marrow blasts (%)	<5	5 - 10	NA	11 - 20	21 - 30
Karyotype	Good	Intermediate	Poor	NA	NA
Cytopenias	0/1	2/3	NA	NA	NA

Median survival by age group (years)

IPSS classification	≤60 (n=205)	>60 (n=611)	≤70 (n=445)	>70 (n=371)
Low (n=267)	11.8	4.8	9	3.9
Intermediate-1 (n=314)	5.2	2.7	4.4	2.4
Intermediate-2 (n=176)	1.8	1.1	1.3	1.2
High (n=59)	0.3	0.5	0.4	0.4

Greenberg, et al.[4]

This widely accepted approach is a useful basis to explain to patients and their families how management may have benefit and balance information against risk.

Subtypes with an excess of primitive marrow precursors have a higher transformation rate to acute leukaemia; this is a feature noted also in chronic myelomonocytic variants. Systematic research has resulted in the current recommendations from the World Health Organization that focus on the number of leukaemic blasts in the marrow and associated cytogenetic abnormalities (Table 2).[2,3]

These features are combined in an international scoring system that has predictive value for survival (Table 3).[4] However, in addition to disease status, there is recent recognition that non-leukaemic deaths may reflect extra-haematological co-morbidity and independently worsen survival patterns. This is particularly so in older patients and should be explained to the patient and the family (Table 4).[5]

Prevalence

This is currently unknown, but males predominate with a median age of 65 years and incidence increases with increasing age.

Aetiology

Genetic factors may have a role in predisposition resulting from genes or polymorphic variants which increase the possibility of developing these entities. There may be a link with marrow injury and possible oxidative stress that accumulates with age, which may lead to mitochondrial damage with mutations in DNA. However, this is controversial.

An association with environmental or occupational factors is documented in

Table 4. Myelodysplasia-specific comorbidity index (MDS-CI)

Variable	Score	
Cardiac disease	2	
Moderate-to-severe hepatic disease	1	
Severe pulmonary disease	1	
Renal disease	1	
Solid tumour	1	
Risk	**Total scores**	**Distribution (%)**
Low	0	65
Intermediate	1 - 2	29
High	>2	6

Della Porta, et al.[5]
Risk stratification based on both disease status and extra-haematological comorbidity in patients with myelodysplastic syndrome.

relatively large case-control studies, but there is no proof of causation. Possible risk factors are tobacco smoking, alcohol, pesticides and a range of organic solvents. Better recognised correlations are the late consequences of cytotoxic chemotherapy and ionising radiation with both high and low concentration of exposure to benzene injurious via marrow damage. Notable is the occurrence after stem cell transplantation and in the course of aplastic anaemia, paroxysmal nocturnal haemoglobinuria and the chronic myeloproliferative syndrome neoplasms.

Children are increasingly recognised as having these disorders, particularly in the setting of Fanconi anaemia, ataxia telangiectasia and Bloom's syndrome. Juvenile myelomonocytic leukaemia and the monosomy-7 syndrome are relatively common; therefore the index of suspicion must be high when faced with otherwise unexplained signs and haematological abnormalities.[3]

Clinical features

Anaemia is present in more than three-quarters of cases and is often symptomatic because of falling haemoglobin levels and coexisting cardiac and respiratory conditions. Erythropoiesis is ineffective and may be compounded by autoimmune haemolysis or pure red cell aplasia. Iron overload frequently occurs as a result of transfusions and increased absorption leading to hepatic, cardiac and endocrine dysfunction.

Thrombocytopenia occurs in more than half of the patients and explains easy bruising and inappropriate mucocutaneous bleeding (Fig. 1). This may be more severe and even lethal in 10 - 15% of cases, particularly in patients who have a poor prognosis according to the international scoring index.
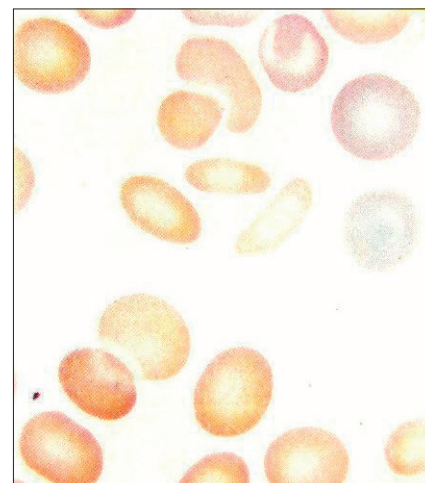
Neutropenic bacterial sepsis, exacerbated by granulocyte dysfunction, responds poorly to standard therapy and remains a major cause of death in 20 - 40% of individuals.

Less frequent occurrences are autoimmune disorders, changes in the skin, inflammatory bowel disease and relapsing polychondritis, splenomegaly and haemostatic disorders.[3,6]

Laboratory findings

Cell morphology is similar to that in nutritional deficiencies such as vitamin B_{12} and folate deficiency, so a careful diagnostic algorithm is vital.

Red cells are macrocytic (Fig. 2) with wide-ranging morphological distortions.[2]

Fig. 1. Easy bruising. Thrombocytopenia is often aggravated by qualitative platelet functional defect. This combination gives rise to a primary haemostatic defect, typically mucocutaneous.
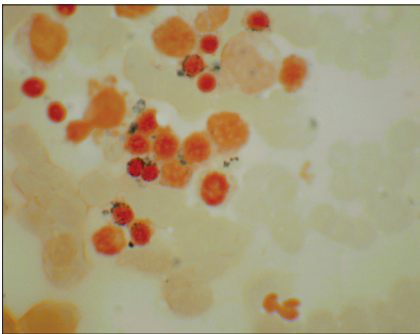

Fig. 2. Dimorphic red cell population. Large and typically oval erythrocytes may, on occasion, include polychromasia, although this feature which reflects the presence of reticulocytes is not usual. Characteristically, a smaller and more normal-appearing population co-exists, but such dimorphism is not uniformly present.

Fig. 3. Ringed sideroblasts. The distinctive arrangement of iron granules around the nuclear membrane characterises this sub-type of myelodysplasia, generally with less aggressive disease course.
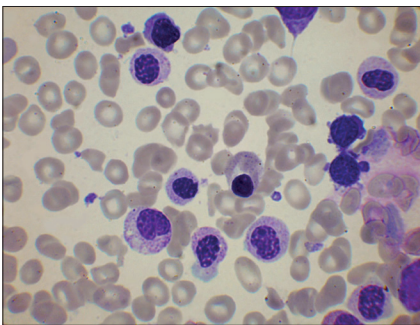

Fig. 4. The dysplastic granulocyte series. Mononuclear, hypogranular neutrophils and pseudo-Pelger-Huët variants with coarse chromatin. These distinctive cytological features are often the initial clue to diagnosis when the well-prepared and suitably stained blood film is examined.
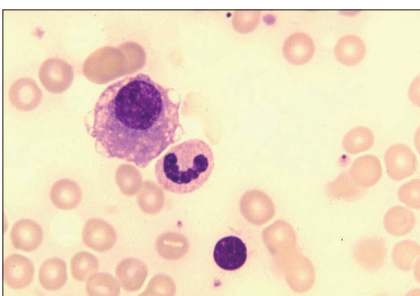

Fig. 5. Megakaryocyte dysplasia. In the marrow these typically very large cells become small and often mononuclear. The same features are often easier to appreciate in a trephine biopsy and virtually diagnostic to the experienced morphologist.

Also present are small cells found in acquired haemoglobin H disease – or alpha thalassaemia. A fast migrating band

seen on electrophoresis and golf-ball like inclusions of the abnormal haemoglobin are shown with supra-vital staining using methylene blue.[2,3]

In the hypercellular marrow dyserythropoiesis is recognised by abnormal nuclear lobulation, irregular cytoplasmic haemoglobinisation together with basophilic stippling. An appropriate iron stain is needed to demonstrate the distinctive and diagnostically important ringed sideroblasts (Fig. 3).

White cells show morphological dysplasia in the form of poor granule formation in the cytoplasm and hyper- or hypo-lobulation of the nucleus (Fig. 4), often resulting in the typical pseudo-Pelger-Huët anomaly. A minimum of 10% dysplastic cells for each lineage is necessary to confidently diagnose these disorders. Monocytes are increased and there are also distinctively abnormal nuclei. A careful cell count is mandatory to record numbers and variations in the leukaemic blast population.

Platelets are typically reduced, although large forms and considerable variation in size are seen. In the trephine biopsy the increased numbers and small size of megakaryocytes, generally mononuclear, are characteristic (Fig. 5). It is important to recognise variants in which fibrous tissue is increased and, conversely, total cellularity is decreased, differentiating from primary myelofibrosis and aplasia respectively.

Making the diagnosis

Unexplained cytopenia, particularly in the elderly and when accompanied by monocytosis, requires a meticulous history aimed at excluding viral infections and nutritional deprivation.

Relatively insignificant bruising and bleeding, unexplained and recurrent infections as well as a broad range of autoimmune manifestations add to the difficulties in recognising this possibility in otherwise well individuals.

However, once considered, the cytomorphology in the peripheral blood and bone

marrow is a reliable diagnostic starting point for an experienced haematologist. Vitamin B_{12} and folate deficiency, toxins, particularly including alcohol and a wide range of medications, as well as HIV infection, need to be excluded. The diagnosis is confirmed by flow cytometry and molecular genetics using fluorescent *in situ* hybridisation and conventional metaphase karyotyping. This information secures the diagnosis and classification as a basis for risk-stratified treatment using the international prognostic scoring system (Table 3).[4] The possible effects of any non-haemopoietic comorbidity also need to be discussed with the patient (Table 4).[5]

Molecular genetics is now an important part of haematology. In the elderly, management needs to take comorbidity into account.[6]

Management

These patients need to be treated only in a properly structured, experienced and effectively functioning multidisciplinary group in a major centre. Therapy should be individualised, based on risk stratification and, where possible, clinical trials.[4,7]

First determine if treatment is necessary, or in an asymptomatic patient decide whether or not a conservative approach is appropriate. Standard supportive care is suitable in all those with a confirmed diagnosis. This is defined as red cell transfusion if symptomatic anaemia is present, with iron chelation, culture-directed antibiotics for documented infection and platelets. There may also be benefit in the simultaneous use of an antifibrinolytic agent such as cyclokapron.

Erythropoietin or similar agents are given, possibly combined with granulocyte stimulating peptides, independent of plasma levels. An adequate trial of therapy is important, probably not for less than 6 months. Thrombopoietin analogues, particularly romiplostim, may be useful.

Where more aggressive intervention is indicated those in the 5q category are treated with lenalidomide.[6,7] The remainder are risk stratified by score on the IPSS.[4] Selected cases with bone marrow failure, rather than leukaemia and particularly when HLA-D 15 positive, may respond to immunosuppression including anti-lymphocyte globulin. This treatment carries risks of infection and infusion-related side-effects that should not be underestimated.[7]

Persisting symptoms raise the possibility of allogeneic immunohaematopoietic stem cell transplantation if clinically appropriate and if a donor is available.[8]

In individuals eligible for this intervention it is still uncertain whether fully myeloablative or reduced intensity preparation, also known as conditioning, should be undertaken first. The benefits of diminishing leukaemic blast count before this procedure are still being debated. The debate is whether such chemotherapy can delay or prevent subsequent disease recurrence. Choice of donor, including possible umbilical cord units, is also under debate.

In those disqualified from this option the low-risk category may qualify for lenalidomide, while more aggressive disease is amenable to DNA methyltransferase inhibition. This approach, together with either newer histone deacetylase agents such as a specific inhibitor, promotes the transcription of genes whose expression has been silenced – the epigenetic approach, which is being investigated by a number of cancer research centres worldwide.[5]

Conclusion

These syndromes are increasingly recognised. It is important that early and accurate diagnosis, with proper risk stratification, is the first step in management.

This crucial initial evaluation is the basis for a carefully defined proactive therapeutic algorithm designed to use all the available resources in an appropriate sequence and setting. It is no longer appropriate to manage these patients outside a comprehensive specialist group that accepts responsibility for all-inclusive care.

References available at www.cmej.org.za

Single suture

Mental health the winner after Breivik 'sane' ruling

Anders Behring Breivik is sane. The verdict pleased the man responsible for the deadliest attack in Norwegian history – but it is also good news for the fight against misconceptions of mental health.

On 22 July 2011, Breivik killed 77 people and wounded 242 others. He said his actions were a protest against a left-wing government that was destroying Norway by promoting multiculturalism.

Many claimed the killings made sense only if Breivik was insane – indeed, an initial psychiatric report diagnosed him as having paranoid schizophrenia. But that highlights misconceptions about mental health, says Tad Tietze of the University of New South Wales in Sydney, Australia, an editor of a book on the attacks. 'People imply that mental-health patients are capable of these acts,' says Tietze. 'They don't deserve to be associated with a fascist mass killer.'

Many of Breivik's statements fit with the views of the extreme right. 'We have to name his ideas for what they are,' says Tietze.

New Scientist, 29 August 2012, online.

References

1. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. The French-American-British (FAB) Co-operative Group. Br J Haematol 1982;51:190-199.

2. Swerdlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon: IARC, 2008.

3. Doll DC, Landaw SA. Clinical manifestations and diagnosis of the myelodysplastic syndromes. www.uptodate.com, 2010.

4. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088.

5. Della Porta MG, Malcovati L, Strupp C, et al. Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. Haematologica 2011;96:441-449.

6. Hellström-Lindberg E, ed. Myelodysplastic Syndromes. Chicago: Remedica, 2008.

7. Stone RM. How I treat patients with myelodysplastic syndromes. Blood 2009;113:6296-6303.

8. Blood Marrow Transplant Rev 2008;18(1).