

## British Society for Haematology Slide Session, Annual Scientific Meeting, Bournemouth, 2000

**Organiser and Chairman:** Dr B.J. Bain

**Expert Discussants:** Dr D. Swirsky and Dr M. Bhavnani

**Case Contributors and Discussants:** Dr M. Layton, Dr N. Parker,  
Dr M. Makris, Dr A. Hendrick, Dr E. Mayne, Dr M.F. McMullin  
and Dr S. Abdalla

### Introduction

The presentation of these cases follows the broad pattern adopted at the BSH Slide Session. Each case is described in turn, appropriate peripheral blood, bone marrow aspirate or other features are shown and the discussants outline their diagnosis. After the presentations, the case contributors present further information, contribute to the discussion and give the final diagnosis. The cases are presented in this manner so that readers can make their own provisional diagnoses, based solely on the information available to the expert discussants.

### Case 1

*Contributed by Dr M. Layton, Kings' College Hospital, London*

The patient was a 10-week-old Egyptian male, delivered at term. He developed neonatal jaundice on day 1 that resolved spontaneously. Pallor was noted from the age of 2 weeks. There was no evidence of iron deficiency. Blood counts at 10 weeks were: Hb 6.7 g/dl, MCV 59 fl, MCH 20.3 pg, reticulocytes 2.7%, platelet count  $1135 \times 10^9/l$ .

The discussant (MB) noted marked anisocytosis and poikilocytosis, including elliptocytes, ovalocytes, fragmented cells and occasional teardrop poikilocytes (Figure 1). There was also basophilic stippling, hypochromia, and polychromasia.

The suggested diagnosis was either homozygosity or compound heterozygosity for hereditary elliptocytosis, leading to hereditary pyropoikilocytosis. The second discussant (DS) concurred. Both discussants wondered

whether the hypochromia might be attributable to a coexistent  $\alpha$ -thalassaemia, as there was said to be 'no evidence of iron deficiency'.

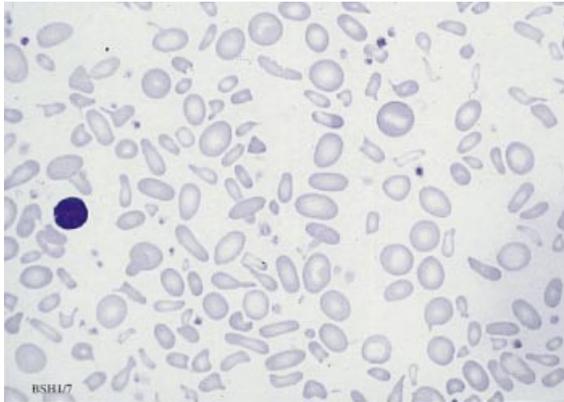
### Case 2

*Contributed by Dr N. Parker, Whittington Hospital, London*

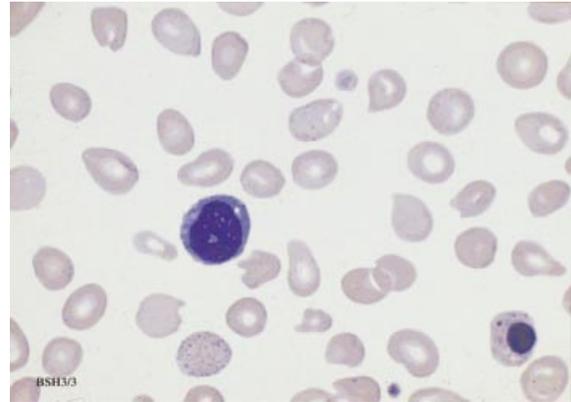
A 51-year-old North European female presented with weight gain and splenic enlargement to 24 cm below the costal margin. Blood count data were: Hb 8.2 g/dl, WBC  $24.8 \times 10^9/l$  and platelets  $369 \times 10^9/l$ .

The case discussant (D.S.) noted an increased white blood cell count. About a third of the cells were blast cells without any particular distinguishing features and another third were primitive cells of megakaryocyte lineage, recognized by their hyperchromatic nuclei, cytoplasmic differentiation and bleb formation (Figure 2a). In addition, there were 7% promyelocytes and myelocytes, 7% neutrophils, 1% eosinophils and 18% basophils. There were 2 NRBC/100 WBC. In addition to mature basophils, there were immature cells with basophil granules (Figure 2b). The red cells showed anisocytosis and poikilocytosis. Platelet morphology was very abnormal, many platelets were abnormally large, hypogranular or both.

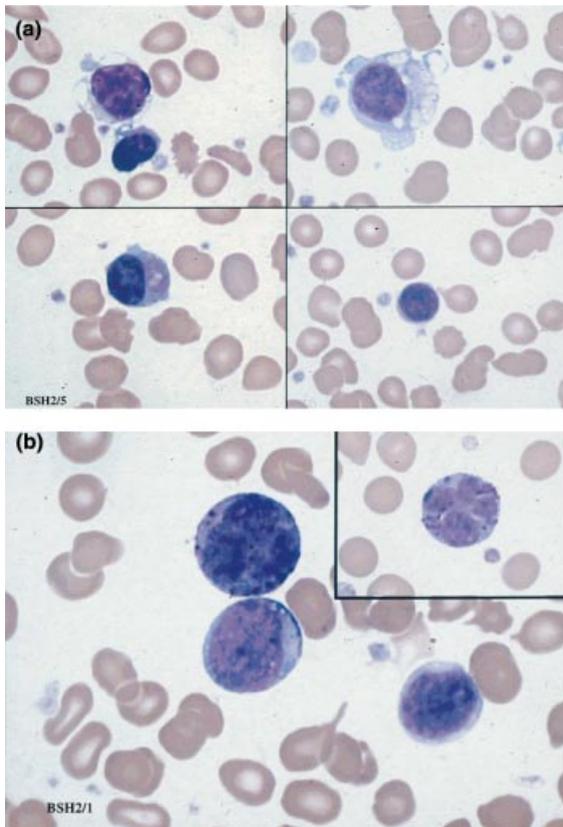
The discussant considered the most likely diagnosis to be Philadelphia-positive chronic myeloid leukaemia (chronic granulocytic leukaemia), presenting in blast transformation with prominent megakaryocytic differentiation. It was not possible from the material available to determine whether the blasts were megakaryoblasts or agranular myeloblasts. A contributor from the audience suggested a diagnosis of atypical, Philadelphia-negative chronic myeloid leukaemia, but in view of the basophilia, the discussant thought it more likely to be Philadelphia-positive. The second discussant (M.B.) concurred.



**Figure 1.** Peripheral blood film, case 1.



**Figure 3.** Peripheral blood film, case 3.



**Figure 2.** (a) Composite picture of five cells in the peripheral blood film, case 2. (b) Peripheral blood film, case 2.

### Case 3

*Contributed by Dr M. Makris, Royal Hallamshire Hospital, Sheffield*

A 17-year-old female with an English mother and a Pakistani father was found to be anaemic when a routine blood count was performed prior to removal of wisdom

teeth. Blood count data were: WBC  $7.9 \times 10^9/l$ , RBC  $3.75 \times 10^{12}/l$ , Hb 8.7 g/dl, MCV 75.6 fl, MCH 23.2 pg, MCHC 30.6 g/dl, RDW 20.6.

The discussant (M.B.) noted marked anisocytosis, microcytosis and poikilocytosis, including elliptocytes, teardrop poikilocytes and occasional irregularly contracted cells (Figure 3). Coarse basophilic stippling, occasional Howell–Jolly bodies and some circulating nucleated red cells were also seen. The most likely diagnoses were thought to be lead poisoning or pyrimidine 5'-nucleotidase deficiency. The second discussant (D.S.) agreed with the morphological observations, but considered congenital dyserythropoietic anaemia or an unstable haemoglobin to be more likely diagnoses. Other suggestions from members of the audience included dominant  $\beta$ -thalassaemia trait and choline phosphotransferase deficiency (Paglia *et al.*, 1983).

### Reference

Paglia D.E., Valentine W.N., Nakatani N. & Rauth B.J. (1983) Selective accumulation of cytosolic CDP-choline as an isolated erythrocyte defect in chronic haemolysis. *Proceedings of the National Academy of Science, USA* **80**, 3081–3085.

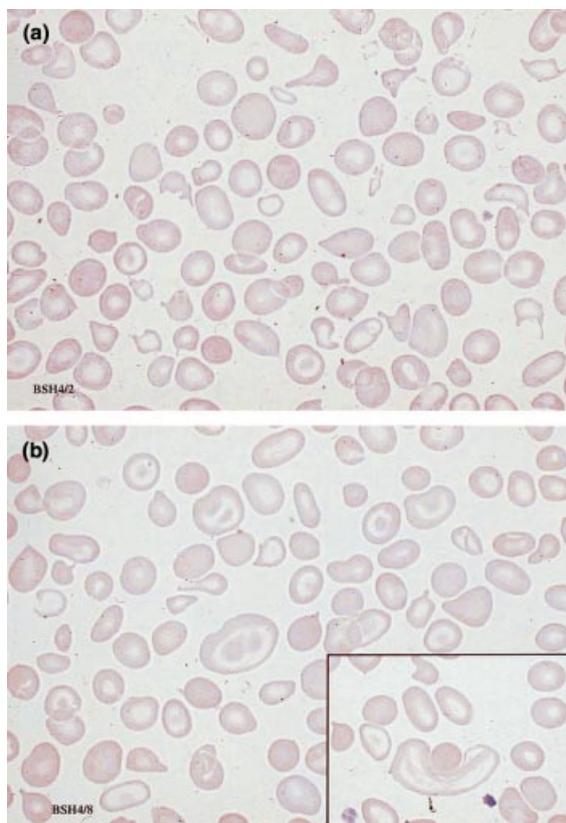
### Case 4

*Contributed by Dr A. Hendrick, South Tyneside Hospital, South Shields*

A 40-year-old male of Hong Kong Chinese ethnic origin presented with hepatosplenomegaly. Blood count data were: Hb 10.5 g/dl, MCV 60 fl, MCH 19.9 pg, platelet count  $50\text{--}75 \times 10^9/l$ . Other laboratory data were: Haemoglobin A<sub>2</sub> normal, haemoglobin F level not increased, ferritin 329 ng/ml, and bilirubin 29 mmol/l (mainly unconjugated). A younger brother with an

almost identical blood picture was found to have  $-\alpha^{3.7}/\alpha\alpha$ , however, the patient has a normal complement of  $\alpha$ -genes.

The discussant (M.B.) noted marked anisocytosis, most cells being microcytic or normocytic with a few definite macrocytes. There was marked poikilocytosis with elliptocytes, target cells, fragmented cells and irregularly contracted cells (Figure 4a). Many cells were normochromic but some were severely hypochromic. The film appearances were considered highly suggestive of haemoglobin H disease, although it was implied in the case history that haemoglobin H had not been detected. As the number of  $\alpha$ -genes was normal a possible nondeletional  $\alpha$ -thalassaemia was considered, for example haemoglobin Quong Sze or haemoglobin Constant Spring. The second discussant (D.S.) was impressed by the presence of some quite large oval macrocytes and some cells with a double stoma, raising the possibility of South-east Asian ovalocytosis, as well as a thalassaemic disorder. A diagnosis of  $\beta$ -thalassaemia or  $\beta$ -thalassaemia/haemoglobin E compound heterozygosity had been considered, but the features appeared atypical. The chairman (B.B.) asked whether



**Figure 4.** (a) Peripheral blood film case 4. (b) Peripheral blood film, case 4, with a view of another field (inset).

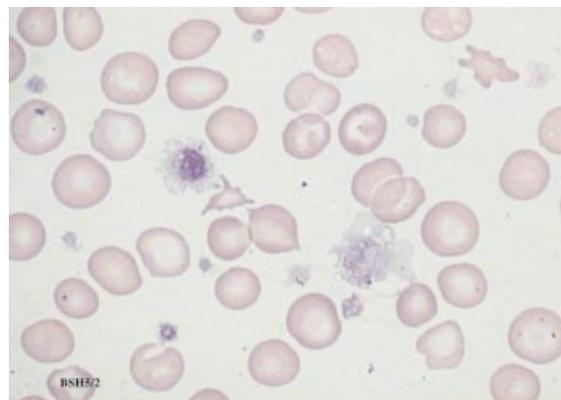
the discussant had considered the possibility of either  $\gamma\delta\beta$ -thalassaemia or coinheritance of  $\beta$ -thalassaemia and  $\delta$ -thalassaemia as a possible explanation of what appeared to be a thalassaemic condition with normal haemoglobin electrophoresis. The discussant had not considered these possibilities.

## Case 5

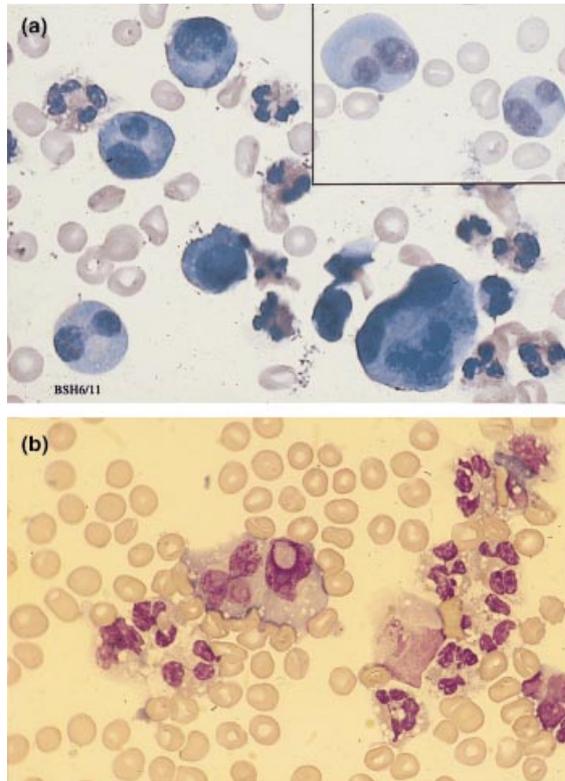
*Contributed by Dr E. Mayne and Dr M.F. McMullin, The Royal Victoria Hospital, Belfast*

A 29-year-old female had initially presented at the age of 10 months with a large haematemesis. She was found to have oesophageal varices and a massive cavernous haemangioma, involving the entire gastrointestinal tract. Splenectomy was performed at the age of 18 months. At the age of 15 years she developed a phaeochromocytoma. She requires occasional transfusions to maintain her haemoglobin level between 5 and 6 g/dl. Typical blood count data were: WBC  $8.7 \times 10^9/l$ , RBC  $2.88 \times 10^{12}/l$ , Hb 5.2 g/dl, MCV 74.7 fl, MCH 18.1 pg, MCHC 24.2 g/dl, platelet count  $852 \times 10^9/l$ .

The case discussant (D.S.) said he found all the features he had expected to find, given the clinical history: a dimorphic blood film, consistent with iron deficiency anaemia post-transfusion, features of hyposplenism and schistocytes, suggesting red cell damage within abnormal vessels. There were some morphological abnormalities of neutrophils and the platelets appeared even larger than would be expected in hyposplenism (Figure 5). The possibility of a myeloproliferative disorder, in addition to everything else, was therefore considered. All things considered, he thought the patient had not just a Kassbach–Merrit syndrome but von-Hippel–Lindau syndrome as well. The second discussant (M.B.) felt there was little left to add.



**Figure 5.** Peripheral blood film, case 5.



**Figure 6.** (a) Peripheral blood film, case 6, with a view of another field (inset). (b) Film of pleural fluid, case 6.

### Case 6

*Contributed by Dr S. Abdalla, St Mary's Hospital, London*

A 67-year-old Indian woman had been under the care of a haematologist for one-and-a-half years. Participants were provided with either a bone marrow aspirate from November, 1999 (performed because the patient had abnormal cells in the peripheral blood) or with a cytopspin preparation of a pleural aspirate from January 2000 (performed because the patient had developed a large pleural effusion). The features shown in the two preparations were essentially similar. Haematological data in November, 1999 were: WBC  $4.9 \times 10^9/l$ , Hb 11.6 g/dl, platelet count  $175 \times 10^9/l$ . Other laboratory findings were: Creatinine, calcium and liver function tests: normal.

The discussant (D.S.) noted that both the bone marrow aspirate and the pleural aspirate contained unusual lobulated cells, sometimes with flower-shaped nuclei (Figure 6a). Some of these cells were very large. Some were binucleate with prominent nucleoli but were not

typical of Reed-Sternberg cells. Some contained large nuclear inclusions (Figure 6b). In addition, there was cytoplasmic basophilia, some cells showing appearances typical of plasma cells. A diagnosis of multiple myeloma was favoured. The second discussant (M.B.) agreed with the morphological observations, but suggested a diagnosis of lymphoplasmacytoid lymphoma. Neither of the discussants thought the features supported a diagnosis of adult T-cell leukaemia/lymphoma despite the striking lobulation of many nuclei.

### Further discussion and final diagnosis

#### Case 1

The case contributor (Dr M. Layton) gave the final diagnosis as hereditary pyropoikilocytosis, although the molecular mechanism was not the one suggested. The mother had hereditary elliptocytosis and reduced red cell membrane  $\alpha$ -spectrin. The father had a normal blood film but was found on molecular analysis (performed by Professor J. Delaunay) to have  $\alpha$ -spectrin Lely, a low expression allele. The condition was therefore due to coinheritance of an elliptogenic mutation and a low expression allele. The case contributor cited *The Haemolytic Anaemias* (Dacie 1985), which refers to hypochromia, presumably due to loss of haemoglobin during the course of fragmentation, as a feature in an early report of severe haemolytic elliptocytosis. The patient initially required blood transfusion but subsequently became transfusion-independent.

### Reference

Dacie J. (1985) *The Haemolytic Anaemias*, Vol. 1. In: *The Hereditary Haemolytic Anaemias. Part 1*. 3rd edn. Churchill Livingstone. Edinburgh, p. 222.

#### Case 2

The chairman reported, on behalf of Dr N. Parker, that the patient had a simple variant Philadelphia translocation, with chromosome 9 appearing normal but both copies of chromosome 22 being abnormal. A *bcr-abl* fusion gene was present, a *b3a2* transcript being detected by multiplex RT-PCR. Splenectomy was performed, the spleen weighed 4090 g. After a period of alternative therapy (di Bella regime) the patient was treated with STI 571 and anagrelide, with a good response. Fifteen months after initial presentation in blast crisis the patient was well.

### Case 3

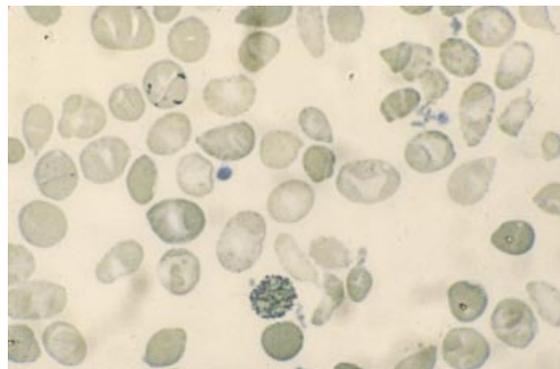
The discussant (M.M.) reported that the patient was clinically well with no hepatomegaly or splenomegaly. Her MCV had been lower on other occasions. Both she and her father had an increased percentage of haemoglobin A<sub>2</sub> but, although both were heterozygous for the IVSI-5 G-C mutation, the patient's father was far less anaemic. Her mother appeared haematologically normal but was found to have duplication of an  $\alpha$ -gene (triple  $\alpha$ ), so that she had a total complement of five  $\alpha$ -genes. Coinheritance of  $\beta$ -thalassaemia heterozygosity and heterozygosity or homozygosity for triple  $\alpha$  is a well-recognized cause of the clinical picture of thalassaemia intermedia.

### Case 4

The case contributor (A.H.) confirmed there was no detectable haemoglobin H on haemoglobin electrophoresis. She reported that molecular analysis (by Dr A. May) showed the patient to be homozygous for nondeletional  $\alpha$ -thalassaemia, specifically haemoglobin Quong Sze. The patient's brother, although phenotypically very similar, was a compound heterozygote for deletional  $\alpha$ -thalassaemia and haemoglobin Quong Sze. Although no haemoglobin H could be detected on haemoglobin electrophoresis, there were occasional inclusion-containing cells on a haemoglobin H preparation (Figure 7).

### Case 5

The case contributor (M.F.McM.) confirmed that the patient had a somewhat atypical form of the von-



**Figure 7.** Haemoglobin H preparation, case 4.

Hippel-Lindau syndrome. In addition to the history as presented, the patient had subsequently developed a pituitary adenoma, then diabetes mellitus and an adrenal mass with space occupying lesions in the liver. The suspected diagnosis was recurrence of the pheochromocytoma with metastases. The case contributor confirmed that the D-dimer level was elevated and that the red cell fragmentation was attributable to fibrin deposition within the abnormal vasculature. It was further reported that it was necessary to maintain the patient's haemoglobin level between 4 and 6 g/dl, as higher levels resulted in severe gastrointestinal haemorrhage.

### Case 6

The chairperson (B.B.) reported on behalf of the contributor (S.A.) that the patient had multiple myeloma with unusual morphology. Other features of the disease were typical.