Case 1

An Active Professional Health Worker with a Serious Genetic Disorder

Patient Details

Age: 44 *Sex:* F
Ethnic background: Mauritius (Creole)
Occupation: Nursing Ward Sister

Reason for Referral

Sickle cell disease.

History and Clinical Findings in Brief

At the age of 30, the patient had a hospital admission because of bone pains. She suffered similar pains on two further occasions, when aged 36 and 39. She had never received blood transfusion. This time she was admitted to hospital with a feeling of "empty-headedness," as though she was about to faint; she also had pain in her left arm, shoulder and back. On examination, the patient looked rather pale but was not jaundiced. The throat and chest were clear. She was found to have a minimally enlarged spleen.

Illustrative Case Studies in Haematology: Red Cell Riddles, First Edition. Lucio Luzzatto and David Roper.

Laboratory Findings

The patient had a moderate microcytic anaemia (see Table 1.1). The blood film confirmed a microcytic picture; i.e. most cells were smaller than normal, and a few cells were exceedingly small (see Figure 1.1). Larger polychromatic red cells (presumably reticulocytes) seemed to stand out as against the predominant hypochromic cells and target cells. "Tear-drop" poikilocytes were also present.

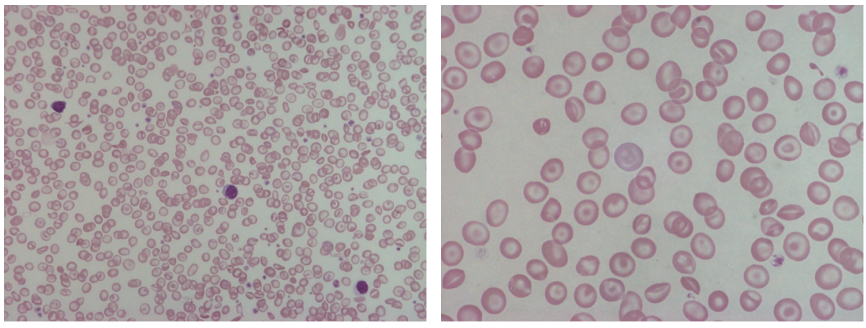
Initial Assessment

This patient reported having sickle cell disease, but she had had relatively mild clinical manifestations. Her level of anaemia would be compatible with homozygous haemoglobin S disease, but her reticulocytes are

Table 1.1 Haematology Data

	Patient	Mother
Hb (g/dl)	8.3	13.4
RBC ($\times 10^{12}$/l)	3.86	7.26
MCV (fl)	66	60
MCH (pg)	21.5	18.5
MCHC (g/dl)	32.7	31.0
RDW (S.D.)	52.5	36.3
Retic (%)	3.0	–
Retic ($\times 10^{9}$/l)	116	–
Hb A_2 (%)	3.5	4.0
Hb F (%)	20.0	1.5
Non-α:α ratio[a]	0.75	0.54 (β:α ratio[a])
$(\beta^S + \beta^A)$:α ratio[a]	0.57	–

[a] Globin chain biosynthetic ratio.



(a) (b)

Figure 1.1 Peripheral blood film: (a) medium power view; (b) high power view.

unusually low and her red cells are very microcytic. In addition, we could not find any sickle cell on the blood film. Thus, it seemed reasonable to suspect a form of sickle cell disease other than homozygosity for Hb S.

Further Investigations

Haemoglobin electrophoresis (see Figure 1.2) showed absence of Hb A with a high level of Hb F which was quantitated at 20%. The Hb A_2 was slightly increased, suggesting co-existing β-thalassaemia trait; but because it was only marginally increased, we felt we ought to confirm this suggestion by globin chain biosynthetic analysis and by testing the mother (the only available member of the family). The blood picture in the mother was typical for β-thalassaemia trait and the β:α biosynthetic ratio was consistent with this (Table 1.1). Thus the patient must have inherited the β-thalassaemia gene from her mother and the beta haemoglobin S gene from her father.

For the sake of completeness, the α-globin status was also assessed (see Figure 1.3). Analysis of the α-globin gene cluster revealed the patient to be heterozygous for α^+-thalassaemia (i.e. α-/αα).

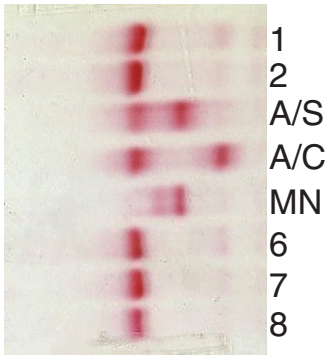


Figure 1.2 Haemoglobin electrophoresis on cellulose acetate membrane; the migration of the haemoglobin fractions is from right to left. An A/S and A/C control are in lanes 3 and 4, respectively. The patient (MN) is in lane 5.

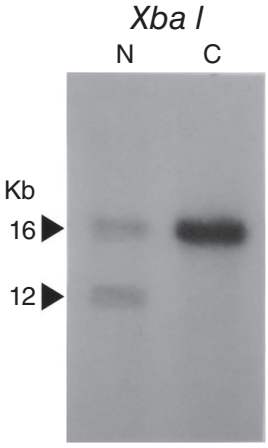


Figure 1.3 Southern blot analysis following an *Xba I* restriction endonuclease digestion of genomic DNA. The normal control DNA (C) yielded a 16 Kb fragment, highlighted by the arrow on the left, when hybridized with an α-globin probe. The patient's DNA (N), in addition to the normal 16 Kb fragment, revealed a smaller size band corresponding to 12 Kb. This is consistent with the patient being heterozygous for deletional α^+-thalassaemia.

Comments

In general, S/β^0 thalassaemia is considerably more severe than S/β^+ thalassaemia [1–3]. However, this patient, a practicing and very active ward sister for most of her working life, although she does suffer recurrent painful episodes especially affecting her limbs, has not had serious complications from her disease: we can designate her S/β^0 thalassaemia as mild. The combination with alpha thalassaemia trait may have ameliorated her sickling disorder; and clearly her erythropoietic system has a high capacity to produce Hb F, which may explain why her Hb A_2 increase is only borderline. Indeed, this patient illustrates the fact that – although S/β^0 thalassaemia is genetically different from S/HPFH – from the clinical point of view the most important determinant of clinical expression is the level of Hb F. At least 3 genetic loci that influence the Hb F level have been identified (*HBS1L-MYB, BCL11A* and the β-globin gene cluster) [4].

Follow-up

Over a 10 year period from the time of presentation, the patient has continued to have a mild clinical course and has never required a blood transfusion.

Conclusion

Sickle cell/β^0 thalassaemia disease with α^+-thalassaemia trait.

Acknowledgements

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Dr. Neville, Hanwell Health Centre, London, UK.

References

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