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Report on Slide Session, British Society for Haematology, 42nd Annual Scientific Meeting, Brighton, 2002

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Each year, at the Annual Scientific Meeting of the British Society for Haematology, there is an educational session in which two experts discuss the morphological features of blood films or bone marrow biopsy sections from patients who have presented a diagnostic problem or who are otherwise instructive. The experts are given no information beyond the brief details provided to all participants who review the slides before the meeting. After the discussants have given their opinions, the case contributor presents further details and gives the final diagnosis. This report follows the format of the meeting so that the reader can reach a provisional diagnosis for him or herself before the definitive diagnosis is revealed.

Case 1

The patient was a 57-year-old Caucasian male who presented with a 3-week history of lethargy, night sweats and weight loss. He was found to have massive hepatosplenomegaly. FBC was: WBC 195×10^9/l, Hb 15 g/dl and platelet count 63×10^9/l. B-cell markers were negative (case contributed by Dr A. Eden, Southend).

The discussant (JM) illustrated medium-sized lymphoid cells with plentiful cytoplasm, azurophilic granules, cytoplasmic vacuolation and slightly irregular nuclei with nucleoli (Figure 1). He favoured an aggressive T-cell leukaemia (Gentile *et al.*, 1994). He felt confident in his diagnosis, as he recognized this case as a patient who had recently been published in the British Journal of Haematology (Gupta, Mills & Eden, 2001). The second discussant (DW) was left with little choice but to concur.

Case 2

The patient was a 6-year-old Greek girl who presented with a 6-day history of fever. She was found to have mild cervical lymphadenopathy and the spleen was palpable 3 cm below the left costal margin. FBC was: WBC 290×10^9/l, Hb 7.3 g/dl, MCV 77 fl and platelet count 307×10^9/l (case contributed by Dr Elene Psiachou-Leonard, Southampton).

The discussant (DW) illustrated marked leucocytosis with neutrophilia, eosinophilia, basophilia and numerous granulocyte precursors (Figure 2). Monocytes were not prominent and dysplasia was minor. He thought that there were no features to suggest that this was reactive, the presence of immature granulocytes was not compatible with a diagnosis of chronic neutrophilic leukaemia and the age and lack of monocytosis did not favour a diagnosis of juvenile myelomonocytic leukaemia or the monosomy 7 syndrome. He thought that, despite the child's age, the findings were totally typical of Philadelphia-positive chronic myeloid leukaemia. The second discussant (JM) was in complete agreement. A member of the audience commented that this type of leukaemia was in fact the most common myeloproliferative disorder

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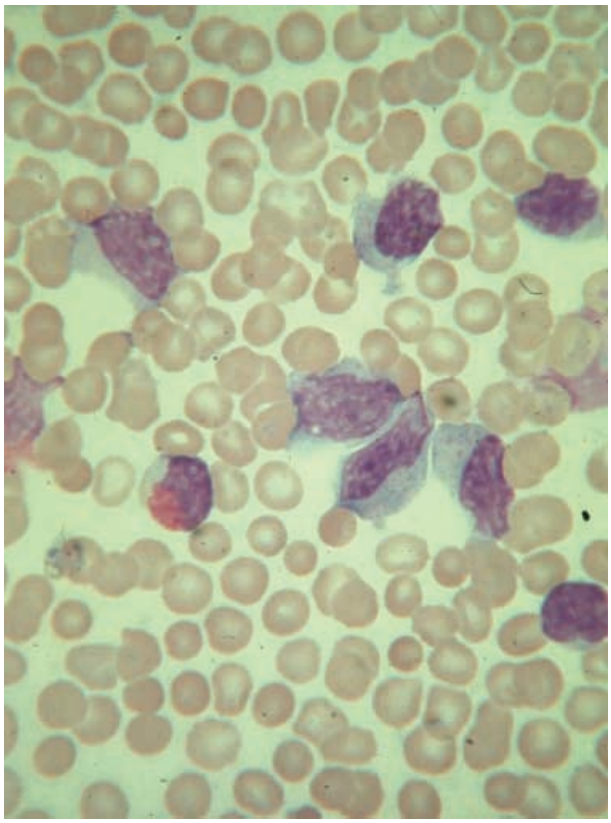

Figure 1. Peripheral blood film from case 1 showing medium-sized, pleomorphic, nucleolated lymphoid cells, some with azurophilic granules.

in children and the discussants should not hesitate to make this diagnosis.

Case 3

The patient was a 70-year-old man with known metastatic carcinoma of the prostate. A routine FBC had shown: WBC 12.9×10^9/l, Hb 11.8 g/dl and platelet count 169×10^9/l. He had moderate splenomegaly but no hepatomegaly or lymphadenopathy (case contributed by Dr Maria Gilleece, Bangor).

The discussant (JM) illustrated lymphoid cells with moderately abundant, weakly basophilic, hairy cytoplasm (Figure 3). The majority of these cells had fairly prominent nucleoli and some appeared to have azurophilic granules. Two per cent of peripheral blood cells were monocytes (monocyte count 0.25×10^9/l). He considered the differential diagnosis to be hairy cell leukaemia, hairy cell variant or splenic lymphoma with villous lymphocytes (SLVL). He favoured hairy cell variant on the grounds of the easily detectable nucleoli and the fairly high count of neoplastic cells. DW was inclined to the view that this was SLVL. A majority of the audience, having heard the discussion, favoured a diagnosis of hairy cell variant but a significant minority favoured each of the other two diagnoses.

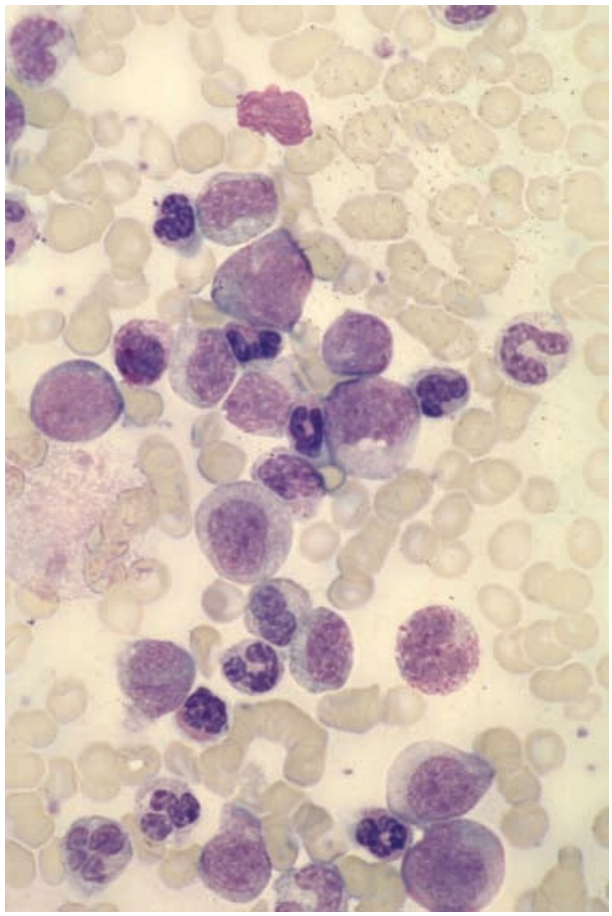

Figure 2. Peripheral blood film from case 2 showing a spectrum of cells from various granulocytic lineages.

Case 4

The patient was a 51-year-old woman with a past history of polycythaemia vera who had been treated with hydroxyurea and had subsequently required splenectomy for progressive splenomegaly. Later in the course of the illness, she had developed a haemorrhagic tendency. The automated platelet count was $15–30 \times 10^9$/l but a manual platelet count was 80×10^9/l (case contributed by Dr V Devalia, Bridgend).

The discussant (DW) illustrated giant, poorly granulated platelets and fragments of megakaryocyte cytoplasm. He thought there were some megakaryoblasts showing cytoplasmic blebs (Figure 4). There was also dysgranulopoiesis with hypogranular and Pelger-Huët forms, hypersegmented neutrophils and macropolycytes. Features of hyposplenism were apparent but teardrop poikilocytes

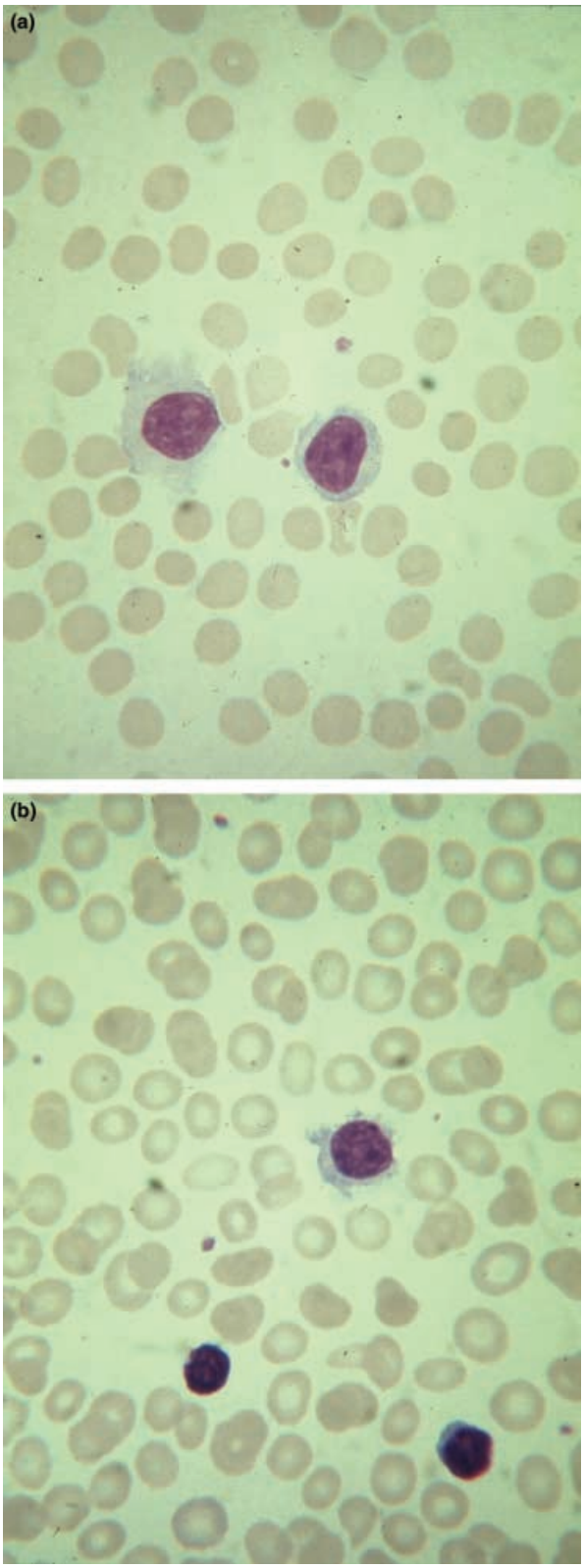

Figure 3. Peripheral blood film from case 3 showing (a) two nucleolated lymphoid cells with plentiful 'hairy' cytoplasm; (b) three lymphoid cells with less cytoplasm but with one of the three having 'villous' cytoplasm and a nucleolus.

were not prominent. He suspected transformation to myelofibrosis or myelodysplasia with a major megakaryocyte abnormality and wondered whether the hypersegmented neutrophils might be the result of hydroxyurea therapy. JM generally concurred but was less impressed by the dysgranulopoiesis.

Case 5

The patient was a 17-year-old boy who presented with a large mediastinal mass and a pleural effusion. FBC was: WBC 6.8×10^9/l, Hb 13.8 g/dl and platelet count 232×10^9/l (case contributed by Dr C. Hatton and Dr Helen Eagleton, Oxford).

The discussant (JM) noted the presence of abnormal medium-sized lymphoid cells with quite marked cytoplasmic basophilia and prominent vacuolation (Figure 5). Some nuclei were slightly indented and rare cells appeared to have a convoluted nucleus. He thought that the differential diagnosis was precursor T-lymphoblastic leukaemia/lymphoma, precursor B-lymphoblastic leukaemia/

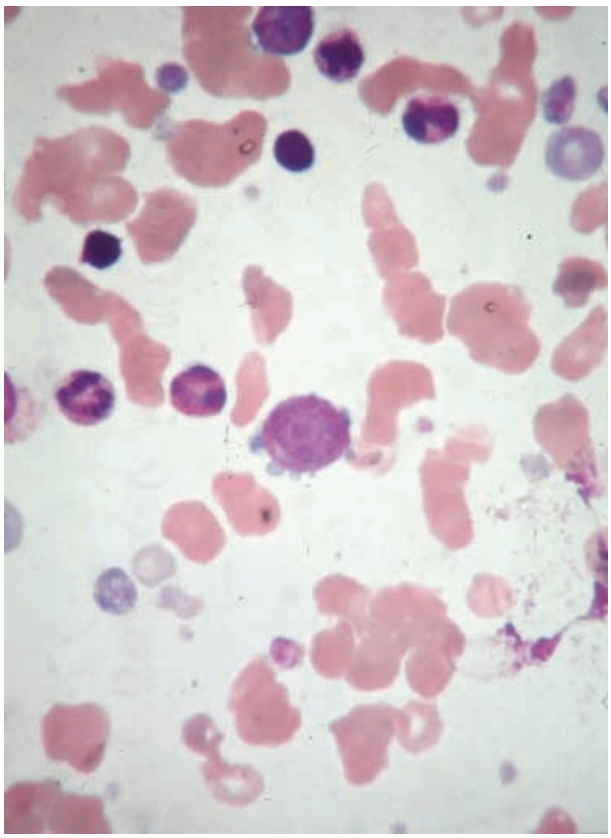

Figure 4. Peripheral blood film from case 4 showing large and agranular platelets and a large immature cell with cytological features suggesting that it is a megakaryoblast.

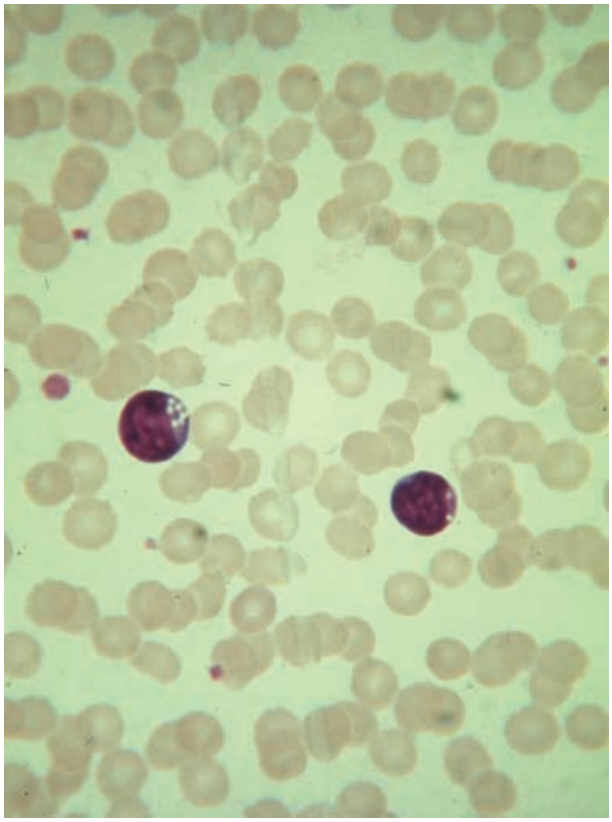

Figure 5. Peripheral blood film from case 5 showing two large immature lymphoid cells with basophilic cytoplasm and cytoplasmic vacuolation.

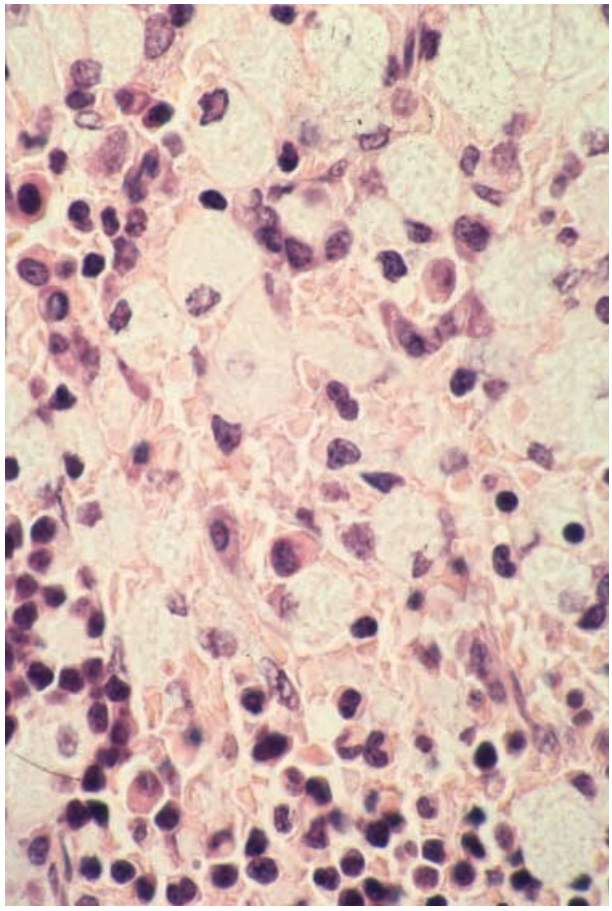

Figure 6. Trephine biopsy section from case 6 showing sheets of altered macrophages with voluminous pale pink cytoplasm.

lymphoma and Burkitt's lymphoma. He considered the possibility of Hodgkin's disease or sclerosing mediastinal B-cell lymphoma but the presence of abnormal cells in the circulation made these diagnoses improbable. The clinical features clearly pointed to a precursor T-lymphoblastic leukaemia/lymphoma but the morphology was rather suggestive of Burkitt's lymphoma. Overall, given that this was a BSH case and nothing is ever straightforward, he thought this would probably turn out to be B-lineage disease DW concurred. He also suspected that a diagnostic trap had been laid and overall he thought this was 'more B than T'.

Case 6

The patient was a 28-year-old Turkish Cypriot man with thalassaemia intermedia who had suffered steadily worsening anaemia and had required splenectomy. He also suffered from osteoporosis. Hb was 6.2 g/dl and MCV 84 fl. The total nucleated cell count was high, as a result of numerous circulating nucleated RBCs (case contributed by S. Rassam, Sidcup).

The discussant (DW) noted that the trephine biopsy sections showed erythroid hyperplasia with clusters of immature erythroid cells; he wondered if these were megaloblasts and if the patient had neglected to take his folic acid. In addition, there were considerable numbers of large macrophages with voluminous pale cytoplasm and eccentric nuclei; some of these appeared foamy (Figure 6). These cells had the appearance of storage cells and he thought the differential diagnosis was between a storage disease (Gaucher's disease or Niemann-Pick disease) and pseudo-Gaucher cells as a result of increased cell turnover. Such cells have been reported in thalassaemia major. He wondered if the bone disease might have been osteolytic lesions as a result of Gaucher's disease rather than osteoporosis. The clinical features did not appear compatible with type A or type B Niemann-Pick disease but the possibility of Gaucher's disease or type C Niemann-Pick disease was not excluded. JM also favoured a storage disease, perhaps Gaucher's disease, rather than the abnormal macrophages representing pseudo-Gaucher cells.

Discussion and final diagnoses

Case 1

The chairman (BB) reported, on behalf of the case contributor (AE), that this was indeed the published case, and commented that the virtues of reading the British Journal of Haematology had been demonstrated. The neoplastic cells expressed CD2, CD3, CD7, CD8, T-cell receptor αβ, CD11b, CD16, CD56 and CD57.

Most patients with T-lineage large granular lymphocyte leukaemia have a disease that runs a relatively chronic course but NK-like T-cell lymphoma is much more aggressive. The patient did not respond to four courses of combination chemotherapy (CHOP regime – cyclophosphamide, doxorubicin, vincristine and prednisolone) and died within 5 months of presentation.

Case 2

BB reported, on behalf of the case contributor (EP-L), that the child had indeed suffered from Philadelphia-positive chronic myeloid leukaemia. The *BCR-ABL* rearrangement had also been demonstrated. BB mentioned that, at a previous session of the conference, Prof. Irene Roberts had reported that 45 children with chronic granulocytic leukaemia had been seen at Hammersmith Hospital, London, in the last 20 years. The youngest reported patient with this disease was only 3 months old.

Case 3

BB reported, on behalf of the case contributor (MG), that the neoplastic cells expressed B-cell markers (CD19, CD20, CD22 and CD23); they expressed CD10 weakly but not FMC7; they expressed two hairy cell markers (CD11c and CD103) but not CD25 and were positive for tartrate-resistant acid phosphatase. The chairman supposed that, if one accepted that consensus represented 'truth', the diagnosis must be hairy cell variant. Prof. D. Catovsky was unable to be present at the meeting but examined the slides. He thought that this was a borderline case, so was difficult to classify with certainty as hairy cell leukaemia or hairy cell variant; the prominent nucleolus (uncommon in hairy cell leukaemia), the lack of expression of CD25 and the lack of monocytopenia might tilt the balance to hairy cell leukaemia variant. The patient declined treatment but remained relatively well with stable peripheral counts and splenomegaly.

Case 4

The case contributor (DV) reported that the patient had developed post-polycythaemia myelofibrosis. She had not been on hydroxyurea at the time the blood film was made. Despite the platelet count of 80×10^9/l and the numerous large platelets, she had developed a marked bleeding tendency. He attributed this to the largely agranular platelets being functionally defective. Cytogenetic analysis had been normal early in the course of the disease but 20q- had been detected later. The patient remained reasonably well, having benefited from thalidomide therapy.

Case 5

HE reported that the patient also had lymphadenopathy. Cytologically similar cells were seen in the peripheral blood, bone marrow aspirate and pleural fluid. The neoplastic cells expressed CD2, CD3, CD5, CD7, CD10 and terminal deoxynucleotidyl transferase (Figure 7). CD19 and CD20 were not expressed. The final diagnosis was therefore precursor T-lymphoblastic leukaemia/lymphoma.

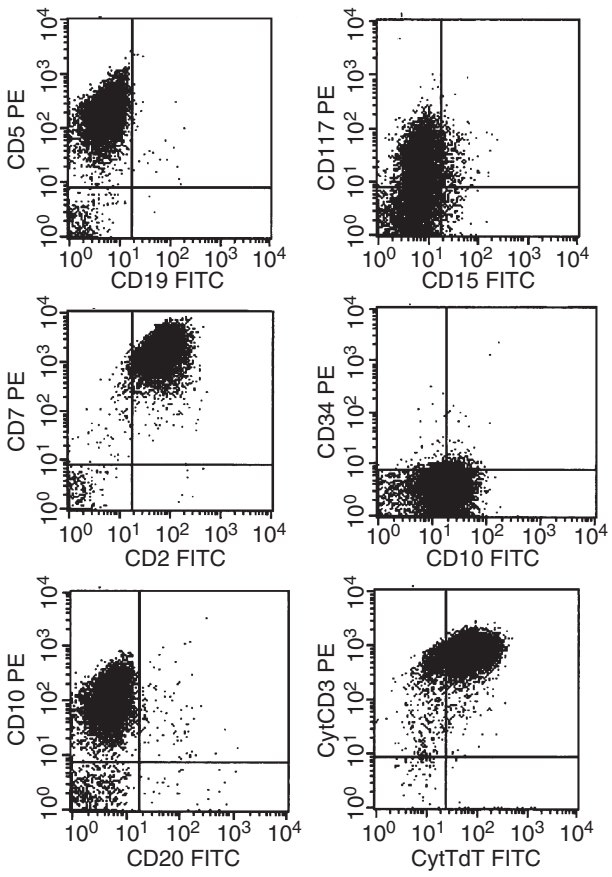

Figure 7. Immunophenotyping of neoplastic cells from case 5.

Subject	Hb (g/dl)	RBC ($\times 10^{-12}$/l)	MCV (fl)	MCH (pg)	MCHC (g/dl)	A_2 (%)	F (%)
Father	12.9	6.16	68	20.7	31.8	6.3	4.8
Mother	13.5	5.87	71	23	32.4	5.8	1
Patient	10.2	5.02	64	20.3	32.4	5.4	77

Table 1. Red cell indices and haemoglobin A_2 and F percentage in the propositus and his parents

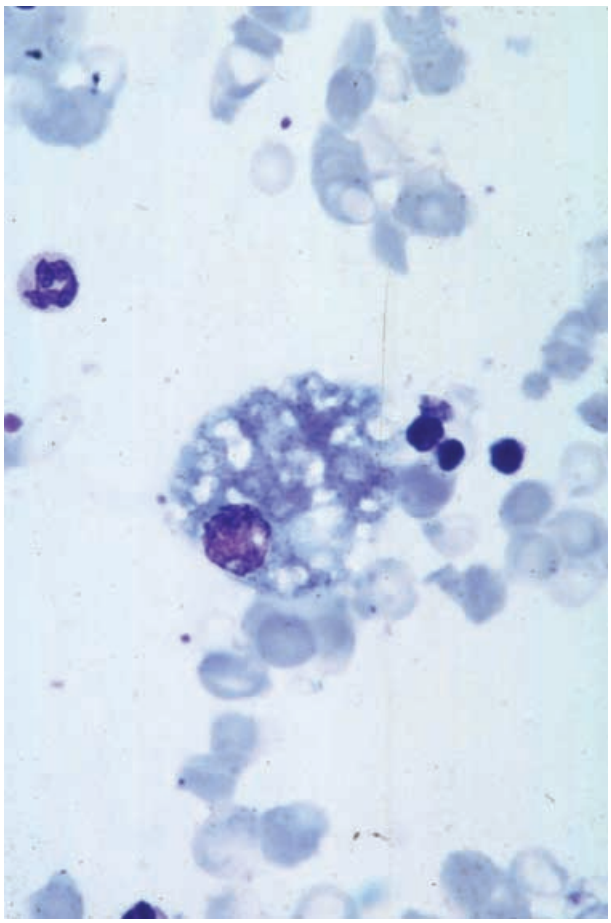

Figure 8. Bone marrow aspirate from case 6 showing a sea-blue histiocyte.

BB commented that if cytological features are suggestive of Burkitt's lymphoma it is important to consider not only precursor T-lymphoblastic leukaemia/lymphoma but also precursor B-lymphoblastic leukaemia/lymphoma associated with t(1;19)(q23;p13) and B-lineage disease associated with t(14;18)(q32;q21) (L3 cytology and mature B immunophenotype).

Case 6

BB reported, on behalf of the contributor (SR), that the case was rather complex and puzzling. Earlier in the course of the illness, the Hb and red cell indices of the patient and his parents had been typical of thalassaemia intermedia and minor, respectively (Table 1). A splenectomy had been performed in 1979, after a Tc^{99} study had shown 19% of red cells to be pooled in the spleen. Thereafter, until 1997, the Hb had been stable around 10 g/dl. The reason for the slow fall in the Hb, associated with a rise in serum ferritin and MCV, that occurred thereafter was not at all clear; assays of serum vitamin B_{12} and red cell folate were clearly normal, as were tests of thyroid and renal function and tests for glucose-6-phosphate dehydrogenase and pyruvate kinase deficiency. He does not have chronic parvovirus infection and no source of blood loss has been identified. Initially, bone marrow storage cells had the features of Gaucher or pseudo-Gaucher cells but a very recent bone marrow aspirate also showed sea-blue histiocytes (Figure 8). Assays of leucocyte enzymes excluded Gaucher's disease, types A and B Niemann-Pick disease and cholesteryl ester storage disease. However plasma chitotriosidase was 1049 nmol/h/ml, a level similar to that seen in type C Niemann-Pick disease. Chitotriosidase, which is produced by monocytes/macrophages, is a very useful surrogate marker of activity in Gaucher's disease; pretreatment levels higher than 20 000 nmol/h/ml are regularly seen, and the levels come down gradually with treatment. Modest elevation of chitotriosidase levels is sometimes seen in other storage disorders, in sarcoidosis and occasionally in thalassaemia major. The abnormal macrophages in this patient are pseudo-Gaucher cells and sea-blue histiocytes as a result of increased cell turnover. Type C Niemann-Pick disease has been excluded by study of cluttered fibroblasts. The cause of the worsening anaemia remains unexplained.

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