

Multidrug resistance and myelomonocytic leukemia in Gaucher's disease

Gaucher's Disease (GD) is associated with an increased risk of haematological malignancies. We present a patient with GD who had a preleukaemic phase prior to developing acute leukaemia. He presented with a negative multidrug resistance (MDR) profile that became positive at relapse.

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Gaucher's Disease (GD) is the most common lysosomal storage disease. It results from a genetic deficiency of the lysosomal enzyme β -glucocerebrosidase causing an abnormal accumulation of glucocerebrosides in macrophages. Type ζ GD is the commonest, defined by the absence of neurologic involvement. Characteristic features include hepatosplenomegaly, skeletal involvement, elevated levels of serum ferritin, acid phosphatase, angiotensin converting enzyme and chitotriosidase enzyme. Treatment consists of enzyme replacement therapy (ERT).¹ Haematological conditions reported in GD include benign monoclonal gammopathy, multiple myeloma, Hodgkin's and non Hodgkin's lymphoma and all forms of leukaemia.²

A male born in 1938 of Ashkenazi Jewish extraction was diagnosed with type ζ (genotype N370S/N370S) GD in 1974 when he presented with splenomegaly and mild thrombocytopenia. Bone marrow (BM) examination revealed classical Gaucher cells and leucocyte assay confirmed a marked reduction in β -glucosidase enzyme activity. In 1997 he presented with fatigue and bruising. Haematological and biochemical data are presented in Table 1. He was commenced on enzyme replacement therapy (ERT) with cerezyme. This promptly improved markers of GD activity with a reduction in spleen size, decrease in plasma chitotriosidase enzyme activity to 251 nmol/h, but there was no significant improvement in the pancytopenia. By January 1999 (Table 1) dysplastic changes affecting all three cell lineages in addition to infiltration by Gaucher cells was observed. A course of intravenous immunoglobulin did not improve the platelet count. He subsequently developed a blood picture compatible with chronic myelomonocytic leukaemia (CMML). In September 2000 (Table 1) the BM contained blasts cells (Figure 1) positive for CD117, CD34, CD13, and CD14 confirming a diagnosis of AML/M4. The plasma chitotriosidase activity rose from late 1999 reaching 877 nmol/h in May 2000. He was enrolled in the UKMRC AML14 trial and randomised to receive DAT (daunorubicin, cytosine arabinoside, thioguanine) plus PSC 833, an inhibitor of P-glycoprotein (P-gp). He achieved a partial remission and proceeded to a second course of combination chemotherapy. His marrow however failed to regenerate adequately. BM analysis revealed a hypoplastic marrow with no residual leukaemic cells. Subsequent cytogenetic analysis revealed trisomy 8 confirming aggressive myelodysplasia. The BM in November 2001 showed 10% blasts; his disease progressed, he was treated palliatively and died in March 2002.

Multidrug resistance (MDR) may arise when cytotoxic agents are effluxed by malignant cells over-expressing P-glycoprotein (P-gp). The MDR profile and drug sensitivity (IC50) on the patient's blast cells were investigated by FACScan analysis and the cell viability assay (MTT) respectively.³ At presentation with AML, the blast cells were rhodamine 123 (R123) efflux negative with normal

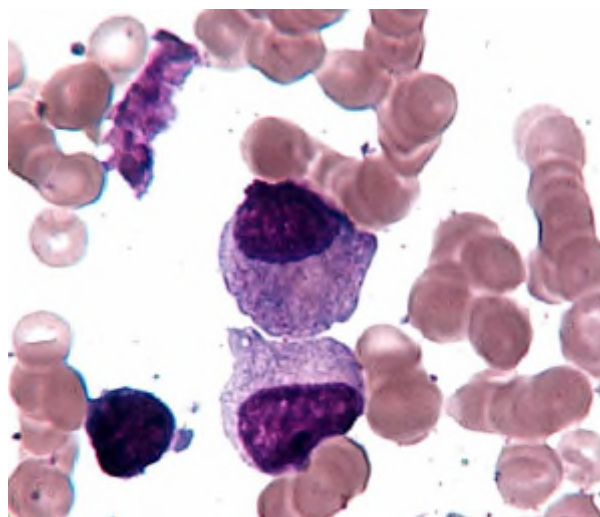


Figure 1 Bone marrow aspirate showing AML blasts cells.

expression of P-gp, multidrug resistance protein (MRP1) and lung resistance protein (LRP). IC50 studies showed sensitivity to daunorubicin. Blast cells at relapse however, showed significant efflux of R123 with overexpression of P-gp (mean cell fluorescence, MCF 2.17 vs 0.94 at presentation, overexpression MCF >1.1) reversible with verapamil, a known inhibitor of P-gp. Expression of MRP, LRP and the IC50 for daunorubicin did not significantly change. The presentation cells were efflux^{-ve}, P-gp^{-ve} and acquired a efflux^{+ve}, P-gp^{+ve} phenotype on relapse after treatment with daunorubicin, a well characterised inducer of MDR. The plasma chitotriosidase enzyme activity that was near normalised with ERT increased coinciding with the onset of AML reflecting increased turnover of cells imposing a burden on the reticuloendothelial system.⁴

All four reported cases of acute leukaemia in GD have developed a myelomonocytic type of leukaemia following myelodysplasia.^{2,5} Our patient is the first to have had his MDR status studied and is the longest survivor. In GD the abnormal accumulation of glucocerebroside in BM, liver and spleen provides constant antigenic stimuli

Table 1 Biochemical and haematological characteristics.

	1997	Jan 1999	March 1999	May 2000	Sept 2000
Hb (g/dl)	13.9	10.9			8.4
wbc ($\times 10^9/l$)	3.3	1.5			21.33
neutrophils (10%)	1.5	1.6			9.47
platelets ($\times 10^9/l$)	30.0	24.0			73.0
serum ferritin (n <146mcg/dl)	702	353			432
acid phosphatase (n <6.2u/l)	10.2	3.0			-
serum chitotriosidase (n <150nmol/ml/h)	1655	448	251	877	-
BM blasts (%)	-	-			24
cytogenetics	-	normal			normal
myeloperoxidase	-	-			+ve
Sudan Black	-	-			+ve

to the immune system which may predispose to lymphoid malignancy.⁶ Similarly, monocytes that are defective due to excess glucocerebroside load could interfere with normal immune regulation. Consequently all cases of AML reported so far in GD are in the myelomonocytic form.

Although GD is rare its association with haematological malignancy is reasonably strong. A retrospective study found a 3.6 and 14.7 fold risk of cancer and haematological malignancy respectively in Jewish patients.⁷ Alterations in ceramide metabolism may affect P-gp mediated drug resistance and that inhibitors of glucosylceramide synthesis may have a role in modulating drug resistance phenotype.⁸ We hope this report and discussion will increase awareness of the risk of haematological malignancy in GD, leading to earlier diagnosis and management.

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