A case of secondary acute myeloid leukemia on a background of glycogen storage disease with chronic neutropenia treated with granulocyte colony stimulating factor

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1 | INTRODUCTION

Glycogen storage disease (GSD) is an autosomal recessive disorder caused by mutations in the SLC37A4 gene on chromosome 11q23. Deficiency in the translocase leads to intracellular accumulation of glycogen and disturbed glycogenolysis and gluconeogenesis.1 Affected individuals require particular dietary regimens, which include uncooked cornstarch (UCCS) as a slowly metabolized, low glycemic source of glucose, which results in less insulin secretion and a lower risk of hypoglycaemia and lactic acidosis.2 Clinical features of type Ib GSD include hypoglycemia, lactic acidosis, hyperuricemia, hyperlipidemia, hepatomegaly, inflammatory bowel disease, and growth retardation.3 GSD type Ib is also associated with neutropenia and neutrophil dysfunction resulting in recurrent infections.4 The introduction of recombinant granulocyte colony-stimulating factor (G-CSF) has improved quality of life and survival to...
adulthood, however, an association with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) has been observed in some cases with congenital neutropenia on G-CSF (Table 1).

We present our experience in the management of a young female with AML on a background of type Ib GSD and chronic neutropenia treated with G-CSF therapy for almost 25 years. We highlight the plausible association between G-CSF and leukemia risk, in a condition that may inherently be associated with an increased risk of AML, and to describe the supportive care required during induction chemotherapy for a patient with this rare metabolic condition.

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| Reference number | Relevance to our case |
|------------------|-----------------------|
| 11               | The first reported case that has described the association between GSD, and AML, however, prior to G-CSF era |
| 12               | The first reported case of a young woman with GSD who was treated with G-CSF therapy who developed AML |
| 13               | Here the young patient with GSD who was on G-CSF therapy had AML with abnormal karyotype. In this case they described monosomy 7 as an associated abnormal karyotype |
| 14               | This was the third reported case that highlighted the link between G-CSF therapy in patients with GSD and AML |
| 15               | The authors of this article have linked telomere shortening with AML in patients with GSD receiving G-CSF in face of the associated neutropenia |

**TABLE 1** Case reports

**FIGURE 1** Bone marrow aspiration showing on the left (A) myeloblasts and dysgranulopoiesis; and on the right (B) showing a myeloblast with auer rod.
pulmonary macro-nodule with ground glass opacity and cavitat-
tion, suspicious for invasive aspergillosis infection. Fiberoptic 
bronchoscopy and bronchoalveolar lavage was planned, requir-
ing the patient to fast overnight prior to the procedure. Consider-
ing her meticulous metabolic requirements, our team consulted 
the metabolic genetics team. Upon fasting, she was started on 
10% dextrose in water with 0.45% saline (D10W-0.45%NaCl) 
by intravenous infusion with serum glucose monitoring every 
3 hours. The IV fluids were titrated to maintain glucose level 
between 4 and 6 mmol/L (70–110 mg/dL). UCCS was 
reintroduced 2 hours following the procedure, and she was 
weaned off IV fluids without incident. Results of the BAL came 
back negative. Due to subsequent progressive worsening of 
the pulmonary cavity, a CT-guided biopsy was performed and the 
pathology report revealed infiltration with myeloblasts: MPO+, 
CD117+ (30%), CD68+ less than 20%, CD34−, with no fungal 
elements. The bone marrow, however, did not show evidence 
of progression. She was diagnosed with a granulocytic sarcoma 
and the decision was made to proceed with induction chemother-
apy using daunorubicin and cytarabine (3 + 7) prior to 
allogeneic SCT.

To address the unique metabolic considerations, the meta-
bolic genetics team provided us with a protocol (Table 2). IV 
medications were preferentially dissolved in normal saline to 
reduce glucose accumulation. There were strict instructions to 
avoid administration of oral glucose or fructose to prevent sud-
den hyperglycemia and insulin secretion. Glucose monitoring 
was performed every 3 to 4 hours and nursing staff and trainees 
were educated on her metabolic requirements and to not admin-
ister: (a) glucagon due to risk of hypoglycemia and lactic acidosi-
s, or (b) lactated Ringer’s solution due to risk of lactic 
acidosis. A dedicated central venous access was inserted and 
reserved solely for the potential need for IV D10W in the event 
of fasting or symptoms that might hinder oral UCCS ingestion.

Radiologic progression (Figure 2A) indicated a diagnostic 
surgical pulmonary wedge resection (Figure 2B). A similar 
strict metabolic protocol was followed due to fasting require-
ments. The excised tissue was free from residual disease. Bone 
marrow aspiration and biopsy showed a hypercellular marrow, 
granulocytic hyperplasia with left shift and some dysplasia 
with less than 4% blasts, indicating regenerative marrow. She 
proceeded to haploidentical SCT. To this date, the patient is 
doing well, almost 14 months posttransplant.

3 | DISCUSSION

GSD type Ib is a rare congenital metabolic disorder that 
manifests with neutropenia and multiorgan dysfunction. The 
Severe Chronic Neutropenic International Registry (SCNIR) 
and The French National Severe Chronic Neutropenia Regis-
try have both conducted individual prospective cohort stud-
ies where transformation to MDS/AML was documented in 
congenital neutropenia syndromes including GSD.6–9 The 
SCNIR reported from their prospectively followed cohort 
4 cases of AML in 83 patients followed for a mean of 
12.2 years, that is, one case per 253 years of G-CSF treat-
ment, a lower rate than for patients with neutropenia due to 
mutations in ELANE, SBDS or HAX1.5,10

A literature search identified four published case reports, 
with ours being the fifth (Table 1). Two were pediatric cases 
and the first preceded the era of G-CSF therapy.11,12 Three 
were adult cases, all exposed to G-CSF (Table 1).13–15 There 
is emerging evidence that prolonged use of G-CSF in patients 
with GSD Ib may lead to marrow stress and telomere shorten-
ing15 which may promote for leukemogenesis. The risk may 
be increased by higher dose G-CSF treatment, and low dose 
therapy has been recommended in this population.1,6

While G-CSF has been the standard therapy for the neutro-
penia in the GSD Ib population, there is increasing evidence 
that the bone marrow is not the primary problem. Several stud-
ies have demonstrated that bone marrow production of cells is 
normal, but apoptosis is occurring in the neutrophils resulting 
in premature death and neutropenia.16,17 Vitamin E supplemen-
tation aimed at lowering oxygen radicals has been found to 
circulate neutrophil numbers and improve clinical 
outcome.18 More recently, Veiga-da-Cunha et al showed that 
failure to eliminate a phosphorylated nonclassical glucose ana-
log (1,5AG6P) is causing inhibition of glycolysis, and treat-
ment with a 1,5-anhydroglucitol-lowering drug successfully 
treated neutropenia in the murine model of GSD Ib.19

G-CSF use in the GSD Ib population has been life sus-
taining, but it is now apparent that it is not treating the 
underlying disorder. Until new therapies are available, we 
recommend vigilant use of G-CSF in this population. 
Patients with GSD appear to have a higher rate of complica-
tions from G-CSF compared with other populations. Hyper-
splenism is almost universal even with low dosing, and the 
incidence of hematologic malignancies may be higher.1,6 As 
a result of the tendency towards infective complications, low 
dose G-CSF therapy has been recommended by consensus 
guidelines. Instead of 5 mcg/kg/day dose that is typically 
used in congenital neutropenia patients, doses administered 
range from 0.5 to 2 mcg/kg/day are typically used in the 
GSD Ib population.1 The consensus guidelines do not rec-
ommend bone marrow testing, but this recommendation 
may need to be reassessed in light of the growing number of 
cases of hematologic malignancies.

In addition to contributing to the growing literature on 
malignancies in GSD, this case report demonstrates the 
meticulous supportive care required for these patients. The 
stress of chemotherapy can induce a metabolic crisis, and 
strict attention to the metabolic requirements of patients with 
GSD is crucial to avoid hypoglycaemia and lactic acidosis.
Table 2  Reference guide for dietary and metabolic management of GSD

| Capillary blood glucose (mmol/L) | Action if patient eating |
|----------------------------------|--------------------------|
| Less than 2.5                    | Give D50W 25 mL IV and recheck every 5 min until blood glucose is above 2.5 mmol/L, then follow instructions below |
| 2.5 to 3.9                       | Give 1 glucose tab and recheck in 15 min; repeat if not above 4 mmol/L. When blood glucose level is above 4 mmol/L, give a carbohydrate snack. |
| 4 to 12                           | No action required |
| Greater than 12                  | NO insulin to be given; inform MD who will assess the route of intake (IV, PO, NG) |

Management of hypoglycaemia

Glucose tablets: keep two packets at bedside to use p.r.n. as per table above:

- If patient is NPO, initiate IV D10W with 0.45% NS and 20 mEq KCl at 110 mL/h.
- Check IV integrity every 2 h to ensure that IV fluid is still running.
- Once diet resumes and the patient has eaten a full meal with cornstarch, reduce IV rate to 50 mL/h for 1 h, then change to saline lock.

Important notes for team, pharmacy and nursing

- Try to minimize steroid use as this will cause significant rise in lactate.
- When necessary, use in lowest dose possible and as short duration as feasible, monitoring blood glucose, lactate and liver function q 4-6 h rather than daily.
- Ensure medications are mixed in NS rather than D5 whenever possible to limit extra source of dextrose.
- Do not administer IV ringler's lactate at any time.
- Glucagon is to be avoided at all times (does NOT treat hypoglycaemia in GSD).
- Do not start IV D10W unless the patient is fasting, unable to eat due chemotherapy adverse effects.

NEVER GIVE GLUCAGON TO TREAT HYPOGLYCEMIA IN PATIENTS WITH GSD
AUTHOR CONTRIBUTIONS

Dina Khalaf: first author, wrote up the manuscript, performed literature review and took the lead in circulating the draft among the co-authors, obtained an informed consent form the patient, as well as submission for publication.

Heather Bell is a clinical dietician who collaborated with Drs. Faghfoury and Morel in drafting of the metabolic protocol (Table 2).

Drs. Vikas Gupta, David Dale, and David Weinstein reviewed and edited the manuscript. Drs. Tierens and Jiong from the hematopathology department provided the slides (Figure 1A, B), and critically reviewed the manuscript. Drs. Santhosh and Maze reviewed the final manuscript and helped with editing.

All of the above mentioned authors had substantial input in draft review, provided good follow up and critical edits to the manuscript, have approved the final draft and they agree to be accountable for this work.

CONFLICT OF INTEREST

There are no competing interests to declare.

PATIENT CONSENT

Patient consent has been obtained. There are no observations on their behalf.

ETHICAL APPROVAL

Approval from the Institutional Committee for Care and Use of Laboratory Animals.

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