TYPE 1 GAUCHER DISEASE PRESENTING AS PERSISTENT THROMBOCYTOPENIA, ASSOCIATED FACTOR XI DEFICIENCY & EMERGENT MYELOMA

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INTRODUCTION

- Gaucher disease (GB) is an autosomal recessive inherited disorder of glycolipid storage
- Caused by absence or low activity of glucocerebrosidase (Gcase) resulting in accumulation of its substrate glucocerebroside in macrophages, termed “Gaucher cells”
- Gaucher cells infiltrate the reticuloendothelial system
- Type 1 GD is pan-ethnic, incidence of 1:100,000 but most common in Ashkenazi Jews (1: 450)
- It is estimated to affect approximately 2-4% of the entire Irish community
INTRODUCTION

- It presents at any age - infancy to adulthood
- Clinical manifestations include hepatosplenomegaly, pancytopenia and bone complications
- Most frequent presentations are with symptomatic splenomegaly or thrombocytopenia
- Thrombocytopenia is caused by hypersplenism and/or bone marrow infiltration by Gaucher cells compromising megakaryopoiesis
CASE PRESENTATION

- 27 year old lady from Lithuania referred to Haematology team, Cork University Hospital with thrombocytopenia in pregnancy (12 weeks)

- Full blood count: **Platelet count - 55 x 10⁹ /L**
  
  Haemoglobin - 10.4 g/L
  
  White cell count – 4.8 x 10⁹ /L

- Past medical history;
  
  - Hepatitis C infection
  - Osteomyelitis
  - Nephritis
  - Chronic thrombocytopenia
  - No significant bleeding history
LABORATORY INVESTIGATION

- Clotting screen:
  - PT 11.2 (9.7-11.3 secs)
  - APTT 36 (23-31 secs)
- Further clotting studies/factor assays performed:
  - Inhibitor screen - negative
  - Lupus screen – normal
  - Antiphospholipid antibodies - normal
  - Von Willebrand screen – normal
  - Factor IX – w/n normal range
  - Factor XII – w/n normal range
  - Factor XI level at 43 % - mild deficiency
LABORATORY INVESTIGATION

- Hereditary or acquired, most commonly factor XI deficiency is an inherited coagulation abnormality
- Her pregnancy proceeded uneventfully & patients platelet count remained stable between $55\, -70\, \times\, 10^9/L$
- She attended Haematology OPD clinic for follow-up;
  - **Persistent thrombocytopenia**
  - Clinical splenomegaly
  - Bone pains and fatigue
- Bone marrow biopsy and peripheral blood morphology was performed
  - Blood morphology; normochromic normocytic anaemia
  - Bone marrow aspirate showed the presence of Gaucher cells
LABORATORY DIAGNOSIS

- Demonstration of the presence of Gaucher cells is not diagnostic of GD

- Pseudo-Gaucher cells/storage cells are morphologically similar thus could be confused with Gaucher cells

- Present in other haematological conditions e.g. chronic myeloid leukaemia, haemoglobinopathies and other storage conditions like Niemann pick disease
LABORATORY DIAGNOSIS

- Measurement of glucocerebrosidase activity in peripheral blood leukocytes

- Chitotriosidase is an enzyme that is overexpressed by Gaucher cells. A prognostic marker useful for indicating disease burden and monitoring treatment of GD

- Patient samples referred to lysosomal storage disease unit, Royal Free hospital, London
  - Glucocerebrosidase 0.2 umol/g/h (1.0-5.0)
    - < 15% of mean normal activity is diagnostic of GD
  - Chitotriosidase 20600 umol/l/h (4.0-120)
DIAGNOSIS - IMAGING

- DEXA scan was performed – normal
- Whole skeletal MRI;
  - Diffuse marrow infiltration
  - Osteonecrosis of humerus (right and left)
  - Established bone infarction
TREATMENT

- 18 month wait before treatment commenced owing to cost; €250,000 a year for ERT

- Patient commenced on Enzyme Replacement Therapy; Velaglucerase, given intravenously at home, twice weekly

- Reduces the accumulation of the toxic substrates

Response to treatment:

- Improved bone pain
- Reduced fatigue
- No new bone lesion and evidence of healing in skeletal disease
<table>
<thead>
<tr>
<th>Laboratory results pre-treatment</th>
<th>Laboratory results post-treatment (~ 20 months)</th>
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<tbody>
<tr>
<td><strong>Full blood count</strong></td>
<td><strong>Full blood count</strong></td>
</tr>
<tr>
<td>Hb: 11.3 g/dl</td>
<td>Hb: 13.4 g/dl</td>
</tr>
<tr>
<td>PLT: 76 x10⁹/L</td>
<td>PLT: 199 x x10⁹/L</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td><strong>Coagulation</strong></td>
</tr>
<tr>
<td>APTT: 37 secs</td>
<td>APTT: 25 secs</td>
</tr>
<tr>
<td>Factor XI: 0.500 IU/ml</td>
<td>Factor XI: 1.110 IU/ml</td>
</tr>
<tr>
<td><strong>Chitotriosidase</strong></td>
<td><strong>Chitotriosidase</strong></td>
</tr>
<tr>
<td>20600 umol/L/hr (4.0-120 umol/L/hr)</td>
<td>935 umol/L/hr</td>
</tr>
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</table>
FACTOR XI DEFICIENCY & GAUCHER DISEASE

- Normalisation of Factor XI levels post treatment indicated that this deficiency was acquired and not inherited.

- In type 1 GD, coagulation abnormalities, in particular deficiency of factor IX and XI are found in a number of patients.

- Consumption of the coagulation factor due on-going low level coagulation activation possibly due to mononuclear cell activation.
MYELOMA & GAUCHER DISEASE

- GD patients have increased risk of developing monoclonal gammopathies in particular multiple myeloma

- Hypothesised mechanism;
  - Gaucher cell resembles an alternatively activated macrophage which is believed to cause hyper stimulation of the immune system
In GD, elevated levels of pro-inflammatory cytokines in particular interleukin 6 (IL-6), may correlate with clonal expansion of B cells. IL-6 is involved in growth and survival of myeloma cells.

Concern about the association of GD and myeloma prompted further laboratory testing:

- Serum protein electrophoresis
- Serum free light chain assay
<table>
<thead>
<tr>
<th><strong>Serum free light chain assay:</strong></th>
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<tbody>
<tr>
<td>Free kappa chains</td>
<td>13.20 mg/L</td>
<td>(3.3 – 19.4)</td>
</tr>
<tr>
<td>Free lambda chains</td>
<td><strong>101.00 mg/L</strong></td>
<td>(5.71 – 26.3)</td>
</tr>
<tr>
<td>Serum K: L ratio</td>
<td>0.13</td>
<td>(0.26 – 1.65)</td>
</tr>
<tr>
<td><strong>Serum protein electrophoresis:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td><strong>18.78 g/L</strong></td>
<td>(6.0 – 16)</td>
</tr>
<tr>
<td>IgA</td>
<td>2.13 g/L</td>
<td>(0.8 – 2.8)</td>
</tr>
<tr>
<td>IgM</td>
<td>1.02 g/L</td>
<td>(0.5 – 1.9)</td>
</tr>
<tr>
<td>Paraprotein level</td>
<td><strong>2.6 g/L</strong></td>
<td></td>
</tr>
</tbody>
</table>
LABORATORY DIAGNOSIS

- Serum calcium - normal
- Serum creatinine – normal
- Haemoglobin – 13.4 g/dl

Diagnosis of monoclonal gammopathy of undetermined significance (MGUS)

- Four month follow-up, patient complaining of increasing bone pain.
- Paraprotein levels and serum free light chains were re-checked:
<table>
<thead>
<tr>
<th></th>
<th>Sept 2015</th>
<th>May 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum free light chain assay:</strong></td>
<td></td>
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<tr>
<td>Free kappa chains</td>
<td>17.30 mg/L</td>
<td>13.20 mg/L</td>
</tr>
<tr>
<td>Free lambda chains</td>
<td>342 mg/L</td>
<td>101 mg/L</td>
</tr>
<tr>
<td>Serum K: L ratio</td>
<td>0.05</td>
<td>0.13</td>
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<td><strong>Serum protein electrophoresis:</strong></td>
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<tr>
<td>IgG</td>
<td>25.81 g/L</td>
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<tr>
<td>IgA</td>
<td>1.17 g/L</td>
<td>2.13 g/L</td>
</tr>
<tr>
<td>IgM</td>
<td>0.76 g/L</td>
<td>1.02 g/L</td>
</tr>
<tr>
<td>Paraprotein level</td>
<td>21.8 g/L</td>
<td>2.6 g/L</td>
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</table>
LABORATORY DIAGNOSIS

Bone marrow biopsy;
- Plasma cells present; >60% in trephine and approximately 30% in aspirate

Immunophenotyping:
- Immunophenotyping detected 12% clonal plasma cells

Skeletal survey;
- Skeletal survey showed new lytic bony lesions

The results were consistent with a diagnosis of multiple myeloma (IgG)
TREATMENT

- Initially the patient was treated with chemotherapy, then underwent an autologous stem cell transplant

- Patient had an excellent response to treatment, now on maintenance chemotherapy

- Continued Enzyme replacement therapy throughout

- Currently clinically very well
CONCLUSION

- Heightened awareness of the association of Gaucher Disease with splenomegaly and unremitting haematological abnormalities like thrombocytopenia may help minimise delayed diagnosis of this rare disease

- Highlight the associated myeloma risk with this disease
ACKNOWLEDGEMENTS

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