Monozygotic twins with hypogammaglobulinemia and chronic active gastritis

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Two monozygotic twin males were born in 1989 after uneventful pregnancy. French Canadians, no consanguinity, no family history of PID.

**Twin 1**
- From birth to 5 years of age
  - 9 otitis media
  - 3 pneumonias
  - 2 cellulitis
  - Infectious mononucleosis at 22 months with mild hepatitis
  - Hypogammaglobulinemia discovered at age 5
    - IgG 117 mg/dL ↓
    - IgA 53 mg/dL ↓
    - IgM 124 mg/dL
    - Complete blood count normal
  - IVIG replacement therapy begun

**Twin 2**
- From birth to 5 years of age
  - Several otitis media
  - 1 pneumonia
  - Hypogammaglobulinemia discovered at age 5
    - IgG 339 mg/dL ↓
    - IgA 137 mg/dL
    - IgM 111 mg/dL
    - Complete blood count normal
  - Negative EBV serology
  - IVIG replacement therapy begun
Despite significant decrease of infections on IVIG
Failure to thrive due to chronic active gastritis diagnosed at age 7

- **Endoscopy:**
  - Focal mucosal erythema and nodularity
- **Histology:**
  - Lymphoplasmocytic and polymorphonuclear infiltrate
- **Undetermined etiology: autoimmune?**
  - H. pylori, EBV, CMV, enterovirus, parvovirus and adenovirus negative
  - No parietal cell antibodies and normal gastrin level
  - Normal colonic biopsies
- **Unsuccessful immunosuppressive treatment**
  - Prednisone, entocort, budesonide
  - Azathioprine, 6-mercaptopurine
- **Necessitates enteral feeding via gastrostomy from age 9**
What is the diagnosis?

Immunologic work-up done in 2005 at age 16 (under IVIG)

Twin 1
- Lymphopenia: 700 $10^6$/L
  - CD3: 609 (87%)
  - CD4: 371 (53%)
  - CD8: 210 (32%)
  - CD19: 7 (1%)
  - CD56/CD3-: 42 (6%)
  - CD31+CD45RA+/CD4: 24%
- IgG: 796 mg/dL (IVIG)
- IgA: <11 mg/dL ↓
- IgM: 12 mg/dL ↓
- Traction bronchiectasis with reduced FEV1 (48%)

Twin 2
- Lymphopenia: 700 $10^6$/L
  - CD3: 581 (83%)
  - CD4: 378 (54%)
  - CD8: 203 (29%)
  - CD19: 28 (4%)
  - CD56/CD3-: 28 (4%)
  - CD31+CD45RA+/CD4: 39%
- IgG: 806 mg/dL (IVIG)
- IgA: 137 mg/dL
- IgM: 148 mg/dL
- Normal pulmonary function tests
Differential diagnosis

- Common variable immunodeficiency
- X-linked disorders
  - X-linked lymphoproliferative disease (XLP)
  - Agammaglobulinemia (Bruton’s)
  - CD40L deficiency (HIGM1)
- Autosomal recessive disorders
  - AICDA and UNG deficiency (HIGM2)
  - CD40 deficiency (HIGM3)
  - Autosomal recessive agammaglobulinemias
- Combined immunodeficiencies
Diagnosis and clinical course

- Markedly decreased iNKT (Vα24 Vβ11/CD3) in both twins
  - 12 /10^6 CD3 (N > 95/10^6 CD3)

- XLP confirmed
  - Lack of amplification of all 4 exons of SH2D1A
  - Xq25 3 megabase deletion by high-resolution genomic profiling
  - Mother identified as carrier

- Rituximab treatment
  - No improvement in gastritis

- Mycophenolate mofetil since 2006
  - Improvement in gastritis
  - Nocturnal enteral feeding continued
# Management issues: hematopoietic stem cell transplantation (HSCT)

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<tr>
<th>Pros</th>
<th>Cons</th>
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<td>- Only definitive cure</td>
<td>- Mortality risk associated with HSCT</td>
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<tr>
<td>- Associated with better survival in a recent historical cohort</td>
<td>- Low risk of HLH at older age</td>
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| - Conservative treatment does not fully protect against:  
  - HLH  
  - Infections  
  - Autoimmune manifestations  
  - Lymphoma | - Conservative management considered satisfactory at the moment |
| - Possibly beneficial for the gastritis | - Uncertain benefit on gastritis |