UNUSUAL CAUSE OF LYMPHOPROLIFERATION

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15 year old boy,

- Second born to a second degree consanguineous parents
- C/O swelling on both sides of neck x 2 months

PAST H/O

History of swellings on both sides of the neck on and off for the past eight years
1999

- Diagnosed to have Mantoux (30mm) positive TB with CXR findings and h/o contact was present

- Took ATT for 9 months
2001

- Axillary node biopsy done in Chennai GH – reported Hodgkin’s lymphoma- lymphocytic predominance type (without IHC)
- Given chemo 1st cycle
- Second opinion on the slide in Chennai private hospital showed atypical lymphoid hyperplasia (with IHC)
- Hodgkins lymphoma ruled out and chemo stopped
2005

- Lymph node biopsy in Chennai private hospital suggested ?Hodgkins lymphoma - not treated

- Lymph node biopsy in April (Tanjore) was reported as Angio Immunoblastic lymphadenopathy

- Was said to have low platelet counts after an episode of malena in 2005 and platelet transfusion done 4 times
2006

- FNAC done twice (private scans and in a private hematology hospital)? granulomatous lymphadenitis
- HPE second opinion showed ?Non Hodgkins lymphoma which was later ruled out by IHC
- Cervical LN biopsy showed T cell proliferation
- Bone marrow- reactive
- Viral screen- negative
His younger sister presented with cervical LAD, was diagnosed with lymphoma at 7 years of age and died after 3 years of treatment with chemo.
ON EXAMINATION:

- Pallor
- Cervical lymphadenopathy - bilateral, firm not matted, massive 5x4 cm

Systemic examination:

- Hepatomegaly of 5 cm (liver span- 11cm)
- Splenomegaly of 3 cm
SUMMARY:

- Adolescent boy with
- Chronic lymphadenopathy
- Hepatosplenomegaly
- Cytopenia
- Confusion about pathology
- Family history of ?Lymphoma
Differential Diagnosis:

- INFECTIONS- TB, HIV
- Immunodeficiency- ?CGD
- Malignancy
- Connective tissue disease- SLE
- Autoimmune lymphoproliferative disease
Salient Laboratory Investigations

- Anaemia (2.2 g/dl)
- Thrombocytopenia (60,000)
- Normal WCC and differential
- Raised ESR (122)
- LFT - 1.0/0.1/9.4/3.4/43/43/93
- Uric acid, LDH - N
- Peripheral smear showed microcytic, hypochromic anaemia, no blast cells
- CXR - N, Mantoux - negative
- HIV negative
Direct Coombs test was positive(3+)
ANA positive speckled (1+)
dsDNA, anti SM ELISA test was negative

**Hypergammaglobulinemia**

- Immunoglobulin G 3426
- Immunoglobulin A 353
- Immunoglobulin M 79
- Immunoglobulin E 941.3
- Lymphadenopathy
- Hepatosplenomegaly
- Family history of ?Lymphoma
- Cytopenia
- Hypergammaglobulinemia
- Autoantibodies (SLE specific dsDNA negative)
- 8 yrs history is against malignancy

ALPS was strongly suspected
Peripheral blood lymphocytes were analyzed by **flow cytometry** for double negative T cells (CD3+ CD4- CD8- DNT).

Healthy control <1% and child’s sample showed **19%** of double negative cells which conclusively proved ALPS.
Counseling of the disease

Child was treated with steroids

During follow up after 2 weeks his lymphadenopathy, hepatosplenomegaly regressed and cytopenias resolved completely.

Currently he is on oral steroids and mycophenolate mofetil and regular follow up for the past 3 months, doing well.
Autoimmune Lymphoproliferative Syndrome (ALPS)

- (ALPS) is an inherited lymphoid disorder
- A primary defect in apoptosis or programmed cell death.
- It results from mutations in molecules involved in the Fas- Fas ligand pathway
- Manifests with cytopenia, lymphadenopathy and hepatosplenomegaly

Criteria for Diagnosis

**Required feature**
- Chronic nonmalignant lymphoproliferation with or without splenomegaly
- Raised (>1%) circulating DNT cells
- Defective antigen induced apoptosis in cultured activated lymphocytes in vitro

**Supportive features**
- Auto immune disease
- Positive family history of ALPS
- Characteristic lymph node or splenic histology
- Mutation in gene coding for Fas

Genetics

- Mutation in gene coding for Fas
- Classification
  - 1a - TNFRSF6 mutation
  - 1b - Fas ligand gene mutation
  - 2 - Caspase 8 or 10 gene mutation
  - 3 - Unknown genetic cause

Jackson CE, et al
Lymph nodes demonstrate marked paracortical expansion of T cells, follicular hyperplasia, plasmacytosis and prominent vascularity of the interfollicular areas.

• Most patients with ALPS present at a young age with lymphoproliferation
• Autoimmune manifestations usually present in early childhood, and may occur months to years after lymphoproliferation

Differential Diagnosis:

- Infections – TB, HIV
- Evans syndrome
- Systemic lupus erythematosis
- Malignancies (lymphomas and leukemias)
- Rosai- Dorfman disease
- Kikuchi- Fujimoto disease
Double negative T cells (DNTs) are normally present in low numbers (<1%) in the peripheral blood and lymphoid tissue. Other auto immune conditions such as SLE and ITP also have mild elevations in DNTs. Marked elevations of DNTs of >5% are described only in ALPS patients.

TREATMENT:

**PREDNISONE**
1mg/kg BD

**MYCOPHENOLATE MOFETIL**

**SIROLIMUS**

**3rd LINE**
VINCristine or
METHotrexate or
MERcaptoPurine or
PYRimethamine/ Sulfadoxine

**REFRACTORY**

(moderate disease)

(severe disease)
Bone marrow (haematopoietic stem cell) transplantation is the only curative treatment for patients with refractory ALPS.

Advances in the management and understanding of autoimmune Lymphoproliferative syndrome (ALPS). *British Journal of haematology*, 148, 205-216.
PROGNOSIS:

- Patients with ALPS are at an increased risk (10-20%) of developing malignancies.
- Most common malignancies are Lymphoma (non-Hodgkin or Hodgkin), Leukemias and rarely solid tumours (thyroid, breast and liver carcinoma).
Literature review

ALPS should also be suspected in children presenting with

- Lymphadenopathy
- Hepatosplenomegaly
- Autoimmunity
- Cytopenias
- Positive family history

for which common causes have been ruled out.
THANK YOU

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