HP education conference
6.21.2011
SH
• **history:** 54 year-old woman with > 5 year history of lymphocytosis

• **past medical history:** hypothyroidism

• **surgical history:** hysterectomy, tubal ligation, appendectomy, knee replacement

• **medications:** Synthroid, Zoloft, Premarin, Chantix

• **social history:** has smoked 1.5 packs per day for 30 years

• **physical exam:** splenomegaly

• **CT abdomen:** splenomegaly (19 cm), no hepatomegaly or lymphadenopathy
lab

• CBC

  14.7
  17.4 ——— 133

  neutrophils  30 %
  lymphocytes  66 %  ALC 11.5
  monocytes    4 %

• immunoglobulins

  IgG 583 mg/dL
  IgA 125 mg/dL
  IgM 1440 mg/dL

• SPE, IFIX

  polyclonal increase in immunoglobulins
lymphocytosis

- chronic lymphocytic leukemia
- splenic marginal zone lymphoma
- hairy cell leukemia
- follicular lymphoma
- mantle cell lymphoma
- viral infection
- *Bordetella pertussis* infection
- stress lymphocytosis
- drug reaction
- persistent polyclonal B cell lymphocytosis
persistent polyclonal B cell lymphocytosis

- persistent lymphocytosis
- binucleated lymphocytes
persistent polyclonal B cell lymphocytosis
clinical features

• 82% women
• median age ~40 years
• 98% smokers
• asymptomatic or minor, nonspecific complaints
• normal physical exam except mild splenomegaly in 10%

persistent polyclonal B cell lymphocytosis
clinical features

• binucleated lymphocytes, whatever the lymphocyte count
• 87% mild lymphocytosis, 17% lymphocyte count < 4 k/μL
• median lymphocyte count 5.45 k/μL (range 2.45-20.52 k/μL)
• binucleated lymphocytes median 4%, range 1-40%
• median serum IgM 6.0 g/L (normal 0.5-2.7 g/L, range 1.2-17.3 g/L)
persistent polyclonal B cell lymphocytosis
peripheral blood morphology

- large lymphocytes
- round, indented or bilobed nucleus or binucleate
- abundant faintly basophilic cytoplasm

persistent polyclonal B cell lymphocytosis
bone marrow

- morphology
  - normocellular (3 cases) or hypercellular (4 cases)
  - intravascular infiltrate of lymphocytes
    - lymphocytes arranged in chains in capillaries or in small clusters in slightly distended venous sinuses
  - interstitial infiltrate
    - less prominent than intravascular infiltrate
  - lymphoid aggregates (3 cases)
    - nonparatra trabecular

- immunohistochemistry
  - intravascular and interstitial lymphocytes predominantly B cells
  - B cells express BCL2 (heterogeneous)
  - B cells CD5, CD23 and CD43 negative
  - lymphoid aggregates predominantly T cells

persistent polyclonal B cell lymphocytosis spleen

- 5 patients with PPBL and progressive splenomegaly, splenectomy in 3
- white pulp marginal zone expansion
- red pulp sinuses infiltrated

persistent polyclonal B cell lymphocytosis
flow cytometry

- polyclonal B cell lymphocytosis in all cases
- CD19+, CD5-

- CD19+, CD22+, CD79+ B cells majority of lymphocytes
- residual CD3+ T cells in some patients
- B cells CD5-, CD43-, CD10-
- surface IgM+, IgD±, IgG-, IgA-
- polyclonal


persistent polyclonal B cell lymphocytosis genetics

• IgH gene rearrangement polyclonal or oligoclonal


• multiple IgH/BCL2 rearrangements in most cases

  – 11 patients 1-7 rearrangements


  – 4 of 6 patients 1-2 rearrangements

persistent polyclonal B cell lymphocytosis

cytogenetics

• performed in 98 cases
• +i(3q) 34% (33 of 98)
• premature chromosome condensation in 8% (8 of 98)
• both abnormalities 31% (30 of 98)
• neither abnormality in 28% (27 of 98)

persistent polyclonal B cell lymphocytosis
FISH

• performed in 84 cases
• +i(3q) detected in 71% (60 of 84)
persistent polyclonal B cell lymphocytosis
cytogenetics and FISH

• 84 cases with cytogenetics and FISH
• +i(3q) detected by FISH in 17 patients with negative cytogenetics
• +i(3q) confirmed in 43 patients with positive cytogenetics
• FISH and cytogenetics negative in 24 cases
persistent polyclonal B cell lymphocytosis

genetic predisposition

• HLA-DR7
  – 6 of 6 cases
  – 19 of 20 cases


• family clusters
  – PPBL in monozygotic twins


  – PPPBL in brother and sister

  – PPBL and multiple BCL2/IgH rearrangements in first degree relatives

persistent polyclonal B cell lymphocytosis follow up

• 111 cases
• median follow up 4.4 years (0.5-29 years)
• stable in 89% (99 of 111)
• decreased lymphocytosis and number of binucleated lymphocytes with persistent +i(3q) in 2 patients 2 years after stopping tobacco use

persistent polyclonal B cell lymphocytosis follow up - deaths

- MI
- cerebral aneurysm rupture
- lung cancer 9 years after PPBL diagnosis
- diffuse large B cell lymphoma
- unknown cause (2 patients)

persistent polyclonal B cell lymphocytosis follow up - malignancies

• lung cancer (2 cases)
• cervical cancer (12 years after PPBL diagnosis)
• diffuse large B cell lymphoma (2 cases, 3 and 9 years after PPBL diagnosis)
• splenic marginal zone lymphoma (3 years after PPBL diagnosis)
persistent polyclonal B cell lymphocytosis
IgM monoclonal gammopathy

• 111 cases, median follow up 4.4 years (0.5-29 years)
• 2 patients had IgM MGUS at time of PPBL diagnosis
• 2 other patients developed IgM MGUS 12 and 22 years after PPBL diagnosis
• no bone marrow biopsy performed
• remained asymptomatic and stable after median follow up of 102 months (range 52-348 months)

summary

• women, median age 40 years
• smoking
• persistent lymphocytosis with bilobed/binucleate cells
• polyclonal B cells
• polyclonal increase in serum IgM
• +i(3q), IgH/BCL2 rearrangements
• HLA-DR7