T-Lymphoblastic lymphoma

But wait, there’s more . . .

A few weeks later the cytogenetics came back . . .
46,XY t(8;13)(p12;q12)[12]
Further Studies

- RT-PCR for FGFR1-ZMYM2 (ZNF 198) positive and confirmed with sequencing
Case #16 - Revised Diagnosis (WHO 2008)

Lymphoid Neoplasm with FGFR1 Rearrangement/ T-Lymphoblastic Lymphoma (8p11 syndrome)
Staging Bone Marrow Exam

- Flow cytometry – negative for lymphoma
- CBC is normal
And the cytogenetics showed .
46,XY t(8;13)(p12;q12)[18]!!!
Diagnosis

Myeloproliferative Neoplasm with t(8;13)
Negative for acute leukemia or lymphoma
So what’s the deal with the t(8;13)?
A Word about the WHO Classification

- Based on:
  - Clinical features (history, physical findings, laboratory data)
  - Morphology
  - Immunophenotype (flow cytometry or immunohistochemistry)
  - **Genetics**

- Recognize and define distinct and coherent clinicopathologic entities
  - The better to study them
  - The better to treat them (the goal)
WHO 2008 Classification

- So, what defines an entity, and what is the “trump card” for the pathologist to make a diagnosis?
- Increasingly, genetics wins
  - We accept a broader spectrum of morphology & immunophenotype when the genetics fits
  - Some entities are essentially solely defined or subclassified by the genetics
    - AML & ALL are subtyped into certain genetic categories
    - PDGFRA, PDGFRB, FGFR1 related neoplasms
8p11 Syndrome

- 8p11 myeloproliferative syndrome (EMS)
- 8p11 stem cell syndrome
- 8p11 stem cell leukemia/lymphoma syndrome
WHO 2008: Classification

- Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1*
  - Myeloid and lymphoid neoplasms with *PDGFRA* rearrangement
  - Myeloid neoplasms with *PDGFRB* rearrangement
  - **Myeloid and lymphoid neoplasms with *FGFR1* rearrangement**
WHO 2008: Definition

- Derive from a mutated pluripotent (lymphoid-myeloid) hematopoietic stem cell with *FGFR1* rearrangement
  - Usually secondary to translocation, t(8;13) most commonly
- Fusion gene encodes an aberrant tyrosine kinase
  - As a rule, these DO NOT respond to tyrosine kinase inhibitors
- Depending on patient and stage of disease, may present as:
  - Myeloproliferative neoplasm (usually chronic eosinophilic leukemia)
  - AML
  - T-lymphoblastic leukemia/lymphoma
  - B-lymphoblastic leukemia/lymphoma
  - Mixed phenotype acute leukemia
WHO 2008: Diagnostic Criteria

- Myeloproliferative neoplasm with prominent eosinophilia and sometimes with neutrophilia or monocytosis
  - OR
- AML or T-LBLL or B-LBLL (usually associated with PB or BM eosinophilia)
  - AND
- Presence of $t(8;13)$ or variant translocation leading to FGFR1 rearrangement in myeloid cells, lymphoblasts, or both
The 8p11 Syndrome

- WHO 2008: Myeloid and lymphoid neoplasms with FGFR1 abnormalities
- Rare neoplasm – 60-70 reported cases
- Age 3-84 years, median 30’s-40’s
  - TCH had the youngest reported case (infant)
  - A fair number (20%) <=18 yrs
- Believed to be derived from a pluripotent stem cell
- May present as:
  - Myeloproliferative neoplasm (chronic phase: CEL or other)
  - AML
  - T or B lineage lymphoblastic lymphoma/leukemia
  - Mixed phenotype acute leukemia
8p11 Syndrome: Clinical Features

- Features vary depending on manifestation (CEL, AML, T-LBL, other)
- 90% will have eosinophilia in PB or BM
  - Our patient did not!
- Those with CEL/other MPN may transform to AML, T-LBL, MPAL, rarely B-LBL
  - Similar to CML model: chronic phase progresses to acute
  - T/B-LBL or myeloid sarcoma in lymph nodes
Pathologic Features

- Vary with presentation – AML, T or B LBLL, MPN (usually CEL), MPAL
- Review of 65 reported cases:
  - Peripheral blood:
    - 92% with peripheral leukocytosis
    - 85% with eosinophilia
    - 10% with relative monocytosis
  - Bone Marrow:
    - 86% with hypercellular marrow, 10% normocellular
    - 71% with increased marrow eosinophils
    - Many with myeloid hyperplasia, some with dysplasia
    - 41% with MPN diagnosed outright

8p11 Syndrome

Variety of partner genes described

- **t(8;13)** most common (48%) – **ZNF198**
- t(8;9)(p11;q33) (17%) – **CEP110**
- t(6;8)(q27;p11-12) (9%) – **FGFR1OP1 (FOP)**
- t(8;22)(p11;q11) – **BCR**
- t(8;19)(p12;q13.3) – **HERVK**
- ins(12;8)(p11;p11p22) – **FGFR1OP2**
- t(7;8)(q34;p11) – **TIF1 (TRIM24)**
- t(2;8)(q37;p11) – **LRRFIP1**
- t(8;17)(p11;q23) – **MYO18A**
- t(8;12)(p11;q15)/dic(8;12)(p11;q11) – **CPSF6**
- t(8;11)(p11;p15) – **NUP98**
8p11 Syndrome

- All cases have rearrangement of *FGFR1* at 8p11-12
  - Translocation in majority; rarely an insertion
- Result in fusion gene and chimeric protein
  - Constitutive activation of the FGFR1 tyrosine kinase
  - Unlike neoplasms associated with *PDGFRA* or *PDGFRB* rearrangements, insensitive to TKIs
8p11 Syndrome: CPC

- **t(8;13)** (*ZNF198-FGFR1*)
  - More often have lymphadenopathy & T-LBL
  - May be bilineal myeloid-T lymphoid
- **t(8;22)** (*BCR-FGFR1*)
  - Higher median age at presentation (61)
  - Mimic CML: leukocytosis with neutrophilia and basophilia
  - Lack of lymphadenopathy
- **t(8;9)** (*CEP110-FGFR1*)
  - Cases of tonsillar involvement
  - Monocytosis
- **t(6;8)** (*FGFR1OP1-FGFR1*)
  - Polycythemia vera & eosinophilia
8p11: Diagnosis

- Conventional cytogenetics
  - Vast majority picked up on routine karyotyping
  - PCR & FISH not routinely performed or clinically available due to rarity

- Immunophenotype of limited use

- Clinical suspicion
  - T-LBL with hypercellular bone marrow or MPN-like picture with eosinophilia very suggestive
8p11 Syndrome: Oncogenesis

- ZNF198-FGFR1 thought to activate AKT and MAPK pro-survival signaling pathways
- Resistant to TNFα induced apoptosis
- Mouse models show a MPN mimicking the human syndrome in bone marrow/blood
  - ZNF198-FGFR1
  - BCR-FGFR1
- T-LBL not seen, but models have impaired T cell development
8p11 Syndrome: Prognosis

- Trisomy 21 most common secondary abnormality
- Generally poor prognosis
- Current TKI and chemotherapy ineffective
- Majority progress to AML (or other acute leukemia)
  - 0-24 months; mean 4.2 months
  - May achieve CR with combination chemotherapy, but usually relapse
- Some successes reported with stem cell transplant
What about our patient?

- T-lymphoblastic lymphoma with t(8;13)
- Staging bone marrow
  - Negative for the lymphoma but
  - Very abnormal architecture, high normal cellularity
  - No eosinophilia, but borderline absolute monocytosis at diagnosis (8/31 & 9/8)
  - t(8;13) is present
- Follow up bone marrow
  - Post chemotherapy changes
  - Negative for lymphoma
  - t(8;13) persists
More Follow Up

- Treated according to AALL0434
  - Lymphoma went into remission
  - Abnormal bone marrow improved morphology, but t(8;13) persistently detected by cytogenetics over next 18 months
- Patient underwent MMUD bone marrow transplant
  - In remission and doing well one year out!