Hematopoietic Tumors of the Nose and Palate

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Why the Nose and Palate?

- Sites that normally have reactive lymphoid tissue
- Small biopsies of even large masses are common
- Close proximity results in similar tumor infiltrates
In the Beginning....

- Hematopoietic tumors of nose and palate
  - Lymphomas
  - Leukemia (chloromas)
  - Plasmacytomas
  - Others
    - Lethal midline granuloma
    - Polymorphic reticulosis

Then Came Immunophenotyping

- Hematopoietic tumors of nose and palate
  - Clarified that most cases considered lymphoma were large B cell lymphomas
  - Did not immediately resolve issues with lethal midline granuloma and polymorphic reticulosis
    - Are they the same?
    - Are they infectious?
    - Are they lymphomas?
      - T, LGL or NK cells?

What We Know Now

- Most cases called nasal lymphoma in the past are diffuse large B cell lymphoma
- Most cases called lethal midline granuloma and polymorphic reticulosis are extranodal NK/T cell lymphoma, nasal type

Sinonasal Diffuse Large B-Cell Lymphoma

- The most common lymphoma to involve the nose in the US
- Most common in 7th decade with a near equal M:F ratio
- Usually associated with sinus involvement
- Tend to invade soft tissue and bone
- Orbital extension common
- Prognosis similar to DLBCL of other sites
Sinonasal Diffuse Large B Cell Lymphoma

NK/T Cell Lymphoma, Nasal Type - Clinical

- Common in Asians and native American populations in the US, Mexico, Central America and South America
- Usually occurs in adults (6th decade) with a male predominance
- Present with nasal obstruction, epistaxis or midline destructive lesion
- Nasal mass commonly involving nose and/or palate with nasal septal invasion
- Adjacent soft tissue invasion, but does not usually start in sinuses

NK/T Cell Lymphoma, Nasal Type - Morphology

- Ulceration is often present, with reactive small lymphocytes, plasma cells, histiocytes and eosinophils
- Proliferation of mixed, variably-sized, irregular lymphoid cells
- Angioinvasive with large areas of necrosis
- Small biopsies may show only necrosis and rebiopsy should be encouraged when a mass is present
NK/T Cell Lymphoma, Nasal Type – Immunophenotype

- Most are true NK cell neoplasms
  - Surface CD3 negative
  - Cytoplasmic CD3ε positive
  - CD2 positive
  - CD5 negative
  - CD56 positive
  - TIA-1, Granzyme B and Perforin positive
  - CD4, CD8, CD16, CD57, and TCR proteins negative
  - CD7 and CD30 variable

NK/T Cell Lymphoma, Nasal Type – Molecular Genetics

- EBV positive by in situ hybridization
EBV positive by in situ hybridization
- EBV LMP1 often not detectable
- EBV is clonal by Southern blot analysis

Most lack TCRG, TCRB and IGH@ gene rearrangements (NK cells)

Chromosome 6 abnormalities most common (del(6)(q21q25) and i(6)(p10))

Deletions or mutations of FAS, TP53, CTNNB1, KRAS, or KIT reported
**NK/T Cell Lymphoma, Nasal Type – Disease Sites**

- Nasal cavity (including nasopharynx and palate)
- Skin
- Soft tissue
- GI tract
- Testis

**NK/T Cell Lymphoma, Nasal Type – Differential Diagnosis**

- Infectious disorders
  - Chronic sinusitis does not cause a mass; lymphoma does
  - Reactive conditions in older adults do not have sheets of EBV-positive cells; NK/T cell lymphoma, nasal type does

- Diffuse large B-cell lymphoma
- Infectious disorders
- T cell lymphomas

- What if it is CD30-positive?
  - If EBV-negative, consider ALCL or other PTCL
  - If EBV-positive, still NK/T cell lymphoma

- What if it is CD56-positive and EBV-negative?
  - If other T-cell markers present (sCD3, CD5, CD4, CD8), supports PTCL

- What if it is EBV-positive and CD56-negative?
  - If NK immunophenotype (sCD3 negative), still NK/T cell lymphoma
NK/T Cell Lymphoma, Nasal Type – Prognosis

- Appears to be location dependent
  - Nasal cavity
    - Poor prognosis when high stage or with marrow involvement
  - Non-nasal sites and low-stage nasal disease
    - Possible better prognosis

Plasma Cell Neoplasms of the Nose and Palate

- Extraosseous (extramedullary) plasmacytoma
- Plasmablastic lymphoma

Extraosseous Plasmacytoma – Clinical Features

- 80% occur in the head and neck, especially in nasopharynx, nose, sinuses and tonsils
- Male predominance occurring most often in 6th decade
- Usually a nasal mass, with signs of obstruction, rhinorrhea and epistaxis
- Represent 3-5% of plasma cell neoplasms
- Must be localized proliferations with no evidence of marrow multiple myeloma
Extraosseous Plasmacytoma – Morphology

- Sheets of plasma cells with abundant eccentric cytoplasm and variable nuclear enlargement or atypia
- Anaplastic types may be difficult to identify as plasma cell lineage
- Usually lack a large cell lymphocyte population

Extraosseous Plasmacytoma – Immunophenotype

- Usually CD20, PAX5 and CD45 negative
- Kappa or lambda Ig light chain positive (clonal), usually expressing IgG heavy chain
- CD138 positive, but should exclude epithelial tumors that may also express CD138
- Subset express CD79a or CD56
Extraosseous Plasmacytoma – Molecular Genetics

- *IGH* and *IGK* gene rearrangements
- Frequency of myeloma-like cytogenetics not well studied
- Not associated with EBV or HHV8

Extraosseous Plasmacytoma – Differential Diagnosis

- Nasopharyngeal carcinoma (NPC) (vs. anaplastic plasmacytoma)
  - NPC is pan-keratin and EBV positive; plasmacytoma is not
- Lymphoma ("immunoblastic", lymphoplasmacytic and extranodal marginal zone lymphomas)
  - Lymphomas usually CD20 and CD45 positive; plasmacytomases are usually not
  - Plasmacytomases usually lack a small B-cell infiltrate
  - Lymphomas are IgM positive; plasmacytomases are IgG or IgA
- Multiple myeloma
- Plasmablastic lymphoma

Extraosseous Plasmacytoma – Prognosis

- Good prognosis
  - 70% disease free at 10 years
- Usually treated with local radiation
- Approximately 15% eventually develop multiple myeloma

Plasmablastic Lymphoma – Clinical Features

- Confusing term that should only be applied to a distinct, but uncommon entity
- Frequently involved palate and gingiva, but may occur at other extranodal sites
- Male predominance usually occurring in 6th decade
- Most cases are associated with HIV or other immunosuppression
Plasmablastic Lymphoma – Morphology

- Oral and nasal cavity cases tend to have a monotonous population of immunoblast-like cells with a prominent nucleolus and abundant cytoplasm (so-called “oral mucosa” type)
- High mitotic rate with tingible body macrophages present

Plasmablastic Lymphoma – Immunophenotype

- CD45, CD20 and PAX5 weak or negative
- CD79a often positive
- CD138 usually positive
- Usually can detect IgG and monotypic light chains
- Ki-67 proliferation rate usually over 90%
- Variable CD30, EMA and CD56

Plasmablastic Lymphoma – Molecular Genetics

- IGH@ and IGK@ gene rearrangements detectable
- EBV in situ hybridization positive
- HHV8 negative
Plasmablastic Lymphoma – Prognosis

- Historically poor prognosis
  - Most dead at one year
- Unclear if outcome has improved or frequency has decreased with improved HIV therapy

Plasmablastic Lymphoma – Differential Diagnosis

- Extraosseous plasmacytoma and multiple myeloma
  - Presence of EBV excludes myeloma/plasmacytoma
- Burkitt lymphoma
  - Burkitt lymphoma is strongly CD20 positive, usually CD138 negative and most US cases are EBV negative
- Primary effusion lymphoma (PEL)
  - PEL may form solid tumor mass, but is HHV8 and often EBV-positive, while HHV8 is not positive in plasmablastic lymphoma
Primary Effusion Lymphoma - Immunophenotype

- Keratin
- CD45
- CD43
- CD30
- CD138
- CD3
- CD20

Plasmablastic Lymphoma – Differential Diagnosis

- Extraosseous plasmacytoma and multiple myeloma
  - Presence of EBV and IgG both exclude myeloma/plasmacytoma
- Burkitt lymphoma
  - Burkitt lymphoma is strongly CD20 positive, usually CD138 negative and most US cases are EBV negative
- Primary effusion lymphoma (PEL)
  - PEL may form solid tumor mass, but is HHV8 and often EBV-positive, while HHV8 is not positive in plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
  - Presence of HHV8 and lack of EBV exclude plasmablastic lymphoma
Large B-cell Lymphoma Arising In HHV8-Associated Multicentric Castleman Disease

Kappa ISH
Lambda ISH

Large B-cell Lymphoma Arising In HHV8-Associated Multicentric Castleman Disease

EBV
HHV8
Large B-cell Lymphoma Arising In HHV8-Associated Multicentric Castleman Disease

Differential Diagnosis of Plasma Cell Tumors

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<th>Diagnosis</th>
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<th>Ig</th>
<th>HHV8</th>
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<td>IgG</td>
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<tr>
<td>Plasmablastic lymphoma</td>
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<td>IgG</td>
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<tr>
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<tr>
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<td>IgM λ</td>
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<tr>
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<td>IgM</td>
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Things to Remember

- Most hematopoietic tumors of the nose and palate form a mass, so clinical history is important
- Other useful history
  - Associated multiple myeloma?
  - Monoclonal serum protein?
  - HIV positive?
- Ask for more tissue when
  - Small biopsy with necrosis or crush artifact
  - Especially if there is a mass
- Serum protein electrophoresis is your friend
  - IgM clones usually support lymphoma
  - IgG or IgA clones support plasmacytoma/myeloma or plasmablastic lymphoma
- EBV LMP1 immunohistochemistry is not enough
  - EBV in situ hybridization is the best means of detecting the virus
Things to Remember

- Don’t rely on CD138 too much
  - Make sure you have more hematopoietic specific markers
- Plasmacytoid tumors of the nose and palate are not all the same
  - Extraosseous plasmacytoma - Good
  - Plasmablastic lymphoma - Bad

Thank you for your attention