EPSTEIN BARR VIRUS ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS IN THE SKIN

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EBV-ASSOCIATED LYMPHOPROLIFERATIONS IN SKIN

A variety of EBV-associated LPDs may involve the skin
  • Primary site of disease
  • Part of more widespread dissemination

Important to recognize and accurately classify
  • Different biology
  • Different treatments
  • May be first indication that patient is immune suppressed

This talk:
  • Brief overview of EBV
  • Discuss specific types of EBV-associated LPD that are encountered in skin
    • EBV+ B-cell LPDs
    • EBV+ NK/T-cell LPDs
EPSTEIN-BARR VIRUS

Human Herpesvirus 4

Ubiquitous:
- Infects vast majority of population in first few years of life
- Symptomatic infection induces EBV-specific cytotoxic T-cell response
- Followed by latent stage
  - Virus persists indefinitely in circulating B-cells
  - Latent state maintained by expression of viral transcripts and proteins

Latent viral proteins also affect host cell:
- Promote cell division
- Inhibit apoptosis

Host immune system
- Recognizes viral proteins and eliminates infected cells
- Keeps viral stimulated B-cell proliferation in check
- This control lost when host immunity compromised
- Result is EBV-driven lymphoproliferation
**Acute/lytic infection**
- EBV infects B-cells
- Viral proteins drive B-cell proliferation

**EBV-specified T-cell response**
- Eliminates viral infected cells

**EBV latency**
- Most viral genes switched off
- Any subsequent viral and cellular proliferation held in check by cytotoxic T-cells
**Latent infection**
- Viral and cellular replication held in check by host immune system

**Immune suppression**
- Loss of EBV specific cytotoxic T-cells
- Viral replication and B-cell proliferation free to resume unchecked
- Results in EBV-driven LPD
EBV+ LPD

EBV infected B-cells

EBV specific cytotoxic T-cells

Latent EBV infection
Immune dysregulation leading to EBV-associated LPDs well documented
  • Organ transplantation (PTLD)
  • Iatrogenic immunosuppression for autoimmune disease
  • HIV infection
  • Congenital immune deficiency

EBV-associated LPDs more recently recognized in apparently healthy patients
  • Many probably the result of immune senescence

EBV-associated LPDs may involve:
  • B-cells
  • T-cells
  • NK-cells
EBV-ASSOCIATED B-CELL LYMPHOPROLIFERATIVE DISORDERS IN THE SKIN

EBV-associated B-cell LPDs encompass a broad spectrum of disease

- Benign self-limiting proliferations
- Polymorphic partially destructive proliferations
  - May spontaneously regress or respond to reduction in immunosuppression but some require more aggressive therapy
- High-grade aggressive neoplasms
  - Very occasional examples undergo spontaneous regression or respond to reduction in immunosuppression
  - Most require multi-agent chemotherapy

EBV-associated B-cell LPDs that may be encountered in the skin include;

- *EBV-positive mucocutaneous ulcer (provisional entity)*
- Lymphomatoid granulomatosis
- EBV-positive diffuse large B-cell lymphoma, not otherwise specified
1. EPSTEIN-BARR VIRUS POSITIVE MUCOCUTANEOUS ULCER
First described as an entity in 2010:

EBV Positive Mucocutaneous Ulcer—A Study of 26 Cases Associated With Various Sources of Immunosuppression

Stefan D. Dojcinov, MD, FRCPath,* Girish Venkataraman, MD,†
Mark Raffeld, MD,† Stefania Pittaluga, MD, PhD,† and Elaine S. Jaffe, MD†

(Reports of lesions that are probably EBV-MCU present in contemporaneous and historical literature)

Localized development of slowly evolving well defined indurated ulcers at mucosal or cutaneous sites

Thought to be a consequence of reduced immune surveillance for EBV
• Elderly
• Patients undergoing therapeutic immunosuppression for CT disease
  • Most frequently methotrexate
• Post-transplant; solid organ > BMTx
PATHOGENESIS

Thought to be consequence of reduced immune surveillance for EBV

• In EBV+ MCU, speculated that immune surveillance is reduced to a level that is only just sufficient to maintain the EBV in a dormant state systemically
  • Age-related immune senescence
  • Iatrogenic immunosuppression

• Exposure to an additional site restricted immune modulating factor tips balance towards a localised EBV driven lymphoproliferation

• Sites at which EBV-infected cells are prevalent (e.g. Waldeyer’s ring) may be particularly prone to this disruption in equilibrium
CLINICAL FEATURES

- Well circumscribed, often painful, ulcerating lesions at mucosal or cutaneous sites
- Oropharyngeal mucosa is the most frequent site of presentation

Cutaneous involvement
- Often peri-oral
- Other acral sites or trunk may be affected

Gastro-intestinal tract
- Any part may be involved
- Patients occasionally present with a variety of abdominal symptoms, including as abdominal emergencies

- No mass lesion is detectable on clinical examination or imaging
- No systemic lymphadenopathy and/or splenomegaly
- EBV-DNA is typically undetectable in peripheral blood, even in post-transplant cases, in contrast to many other types of EBV-associated lymphoproliferative disorders

Drs Soumya Pandey, University of Arkansas, SH/EAHP LWS case SH2015-0344
M74, 2-month history of ulcerated nasal lesion
PATHOLOGICAL FEATURES

Shallow sharply circumscribed ulcers

Polymorphous infiltrate
  • Lymphocytes – small lymphocytes concentrated at ulcer base
  • Immunoblasts
  • Plasma cells
  • Eosinophils
  • Histiocytes

Reed-Sternberg-like cells
  • Variable numbers

‘Plasmacytoid’ apoptotic cells
  • Abundant basophilic cytoplasm
  • Radial distribution of clumped chromatin in apoptotic nuclei

Angioinvasion
  • Present in 6/26 cases in original series
  • Large lesional cells infiltrating medium sized arteries
  • Surrounding necrosis
**IMMUNOPHENOTYPE**

Immunoblasts and RS-like cells are EBV infected B-cells

- CD20+ (can occasionally be –ve; 3/26 cases)
- CD79+
- PAX5+
- CD30+
- CD45+
- MUM1+
- OCT2/BOB1: majority positive for both
- EBER+
- LMP1+ (usually type II or type III latency pattern)
- CD15+ in 10/23 cases in one series, 0/7 in another)

Many small T-cells in background and surrounding base of infiltrate

- CD4+ & CD8+
- Scattered CD8+ intermediate/large lymphocytes
CD30

CD20

CD30

CD3

EBER
CLINICAL HISTORY

- M72
- Liver transplant 14 years previously
- Recent excision of minimally invasive SCC left retromolar region
- Subsequently developed ulcer at site of operation
- Biopsied

CD30

CD3
MUCOCUTANEOUS ULCER, EBV+
• Spectrum of morphologies and phenotypes

BLAST CELLS MAY BE NUMEROUS: MIMIC DLBCL

SH2015-0206: Dr Grogg
Mayo Clinic

• F49, rheumatoid arthritis on methotrexate
• Ulcerated lesion at corner of mouth
• Excised and methotrexate discontinued
• CR with no relapse
MAY BE ANGIOCENTRIC GROWTH

SH2015-0153: Dr Quintanilla-Fend
University of Tuebigen

- M64; CML on Imatinib
- Ulcerated anal lesion
- Imatinib stopped + Rituximab: CR
SH2015-0072: Dr Dhesi
F77, 1 year history of oral ulcer
Previous small B-cell lymphoma and ITP
Rituximab in 2004 and 2011

MAY RESEMBLE CLASSICAL HODGKIN LYMPHOMA
MOLECULAR

PCR studies

• Monoclonal IG gene rearrangement in 7/18 (40%)

• Monoclonal TCR gene rearrangement in 6/16 (37.6%)
• Oligoclonal TCR gene rearrangement in 5/16 (31.2%)
  • T-cell response = restricted but reactive
  • Reflects reduced T-cell repertoire

Dojcinov SD et al, Am J Surg Pathol 2010
TREATMENT / OUTCOME

- Indolent course although response to treatment may be variable
- Spontaneous regression in a proportion
- For some patients surgical resection sufficient
- Withdrawal of MTx / Azothoprine or reduction in immunosuppression may be required
- Single agent Rituximab probably the most ‘aggressive’ therapy necessary
- Patients who have persisting lesion and/or run a relapsing and remitting course do not seem to progress to more widespread disease
2. LYMPHOMATOID GRANULOMATOSIS
LYMPHOMATOID GRANULOMATOSIS

Angiocentric/angiodestructive EBV-driven lymphoproliferative disease

- 1st described by Liebow and colleagues in 1972
  (Liebow AA et al, Hum Pathol 1972)
- Not recognised as a B-cell LPD until 1974
  (Guinee DG Jr et al, AJSP 1994)

Rare

Most cases seen in adults (mean age = 48 years) but can occur in children

M>F, 2:1

PATHOGENESIS

Most cases associated with underlying immunosuppression

- **Hereditary**
  - Wiskott-Aldrich syndrome
  - X-linked lymphoproliferative syndrome
  - Common variable immune deficiency

- **Acquired**
  - Human immunodeficiency virus
  - Allogeneic organ transplant*
  - Other immunosuppressive drugs*
    - Methotrexate
    - Imatinib
    - Fludarabine

- **Prior history of malignancy in some**
  - Lymphoma
  - ALL/AML
  - Carcinoma

- **In absence of overt cause, usually evidence of impaired immunity on specific testing, e.g.**
  - Abnormal T-cell subsets in peripheral blood
  - Impaired T cell response to skin test antigens

* Cases such as these may be better classified as something else

Sites of involvement

- Lung >90%
- Skin 20-50%
- CNS 26%
- Kidney 32%
- Liver 29%

Symptoms
Related to site of involvement

- Cough
- Dyspnoea
- Chest pain
- Neurological symptoms

Signs
CXR:

- Multiple nodules
- Mostly affecting lower lobes

Variable appearance to skin lesions/.......

Katzenstein A-LA et al, AJSP 2010
Cutaneous manifestations

- Erythematous nodules / papules +/- ulceration
- Indurated plaques
- Folliculitis-like eruptions
- Superficial ulcerations

PATHOLOGY

**Histology**
- Nodular mixed mononuclear cell infiltrate
  - Small lymphocytes
  - Variable numbers of large lymphoid cells
    - Immunoblast-like
    - Rarely Reed-Sternberg-like
  - Histiocytes
  - Plasma cells
- Neutrophils and eosinophils usually absent
- NO granulomas
- Infiltration of blood vessel walls
- Varying degrees of necrosis

**Immunophenotype**
- Background small lymphocytes
  - T-cells;
  - CD4 & CD8/cytotoxic molecule+
- Large neoplastic blasts
  - CD20+
  - CD30+/-
  - EBV+; EBER+, LMP1+/-
  (some series include cases that are EBV-)

**Clonality**
- Reported incidence depends on grade
  - Most grade 2/3 cases clonal IG gene rearrangement by PCR
  - Lower incidence in grade 1 lesions
**GRADING**

**Grade I:**
- Inconspicuous blast cells; often only seen with IHC
- &lt;5 EBV+ cells / hpf by in situ hybridisation
- Only focal necrosis if any

**Grade II:**
- Occasional blasts, sometimes in small clusters
- Usually 5-20 EBV+ cells / hpf; variable, may be up to 50 /hpf
- Necrosis more common

**Grade III:**
- Polymorphic background still present
- Numerous large atypical cells; may form small confluent sheets
- &gt;50 EBV+ blasts / hpf
- Usually extensive necrosis

**N.B. sheets of large atypical EBV+ cells without polymorphous background = DLBCL**

Some cases wax and wane over time and may even spontaneously regress.

Most cases pursue an aggressive clinical course:
- Median survival <2 years quoted in historical series

Some evidence that lower grade lesions respond to less toxic therapy.

Grading dictates treatment, e.g. current NCI phase 2 trial:
- Grade 1: IFNα
- Grade 2: IFNα
- Grade 3: DA-EPOCH-R (R-CHOP in WoSCAN)
3. EBV-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA
   (NOT OTHERWISE SPECIFIED)
EBV-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA

EBV+ proliferations of large B-cells (blasts) in apparently immunocompetent individuals

Originally designated EBV+ DLBCL of elderly (>50 years)
  • Though to be consequence of immune senescence
  • Very poor prognosis

More recent studies report pathologically similar lesions in young individuals
  • Better survival than in elderly

In elderly age group:
  • Higher incidence reported in some East Asian populations c.f. Western populations
    • 8.7-11.4% vs <5%
  • Presents at extranodal sites in 70% patients
    • Virtually any extranodal site may be involved
    • Includes skin
  • Lymph nodes usually also involved
PATHOLOGY
Proliferations composed mainly of blast cells – lacking full range of B-cell maturation

TWO MAIN PATTERNS

Polymorphic
- Blasts have variable appearance
  - Centroblasts
  - Immunoblasts
  - Plasmablasts
- Variable component of reactive cells
  - Lymphocytes
  - Plasma cells
  - Histiocytes

Monomorphric
- Monotonous sheets of large transformed cells

FEATURES COMMON TO BOTH
- Reed-Sternberg-like cells
- Angiocentric/angiodestructive growth
- Necrosis
- Patterns may be mixed within one tumour
PHENOTYPE

B-cell antigen positive
- CD19
- CD20
- CD79a
- PAX5

Post-germinal centre phenotype
- CD10-
- BCL6+/-
- IRF4+

Also positive for:
- CD30
- Bcl2

Type III latency pattern the norm
- EBER+
- LMP1+
- EBNA2+
TREATMENT / OUTCOME

Aggressive disease in patients >50 years
- Responds poorly to conventional treatment for DLBCL (R-CHOP)

Young patients have much more favourable outcome

Nicolae A et al, Blood 2015.126.863-72
OTHER EBV+ B-CELL LPDS MAY INVOLVE SKIN

- Post-transplant lymphoproliferative disorders
  (including cutaneous marginal zone lymphoma)
- EBV+ B-cell proliferations in angioimmunoblastic T-cell lymphoma
- Plasmablastic lymphoma
DIFFERENTIAL DIAGNOSIS
D/Dx EBV+ MUCOCUTANEOUS ULCER FROM OTHER EBV+ B-CELL LPDs:

1. **CIRCUMSCRIPTION IS IMPORTANT PART OF DIAGNOSIS**

   **SH2015-0072: Dr Dhesi**  
   University of Michigan

   ![Image 1](image1.png)

   **SH2015-0169: Dr Nicolae**  
   National Institute of Health

   ![Image 2](image2.png)

2. **CLINICAL CORRELATION ESSENTIAL**
   - Solitary lesion without mass
   - No lymphadenopathy or organomegaly
   - Peripheral blood EBV DNA negative
D/Dx LYMPHOMATOID GRANULOMATOSIS FROM EBV+ DLBCL

1. **PATHOLOGY MAY BE VERY SIMILAR/INDISTINGUISHABLE**

   - Grade 1/2 LyG has prominent background of small T-cells
   - Grade 3 LyG treated as DLBCL

2. **CLINICAL CONTEXT ALL IMPORTANT**

   Only confidently diagnose LyG if typical clinical features
   i.e. bilateral nodular infiltrate in lower lobes +/- other extranodal sites
EBV-ASSOCIATED NK/T-CELL LYMPHOPROLIFERATIONS IN SKIN

EBV-associated NK- and T-cell LPDs may involve the skin, although less common than EBV+ B-cell LPDs
- Relatively rare in Europe and North America
- More prevalent in Central/South America and Asia

As with EBV+ B-cell LPDs they display a spectrum of clinical behaviour
- Indolent self-limiting disease
- Highly aggressive rapidly fatal neoplasm

Entities to be discussed
- Hydroa-vacciniforme-like lymphoproliferative disorder
- Extranodal NK/T-cell lymphoma, nasal type
1. HYDROA VACCINIFORME-LIKE LYMPHOPROLIFERATIVE DISORDER
HYDROA VACCINIFORME-LIKE LPD: BACKGROUND

• EBV can infect T- and NK-cells in some patients during acute infection (more usually infects B-cells)

• EBV-associated T- and NK-cell lymphoproliferative disorders are well documented:
  • Majority of these occur in patients from East Asia and Latin America, include:
    • Chronic active Epstein-Barr virus infection (CAEBV)
    • T-cell lymphomas that may follow CAEBV infection
    • Extranodal NK/T-cell lymphoma of nasal type
    • Aggressive NK-cell leukaemia
    • Subset of peripheral T-cell lymphomas (often in the context of impaired immunity)
CAEBV of T/NK cell type shows a broad spectrum of clinical manifestations

- Indolent, localised, self-limiting proliferations
- Aggressive and often fatal systemic disease characterised by
  - Fever
  - Hepatosplenomegaly
  - Lymphadenopathy

A proportion of cases within this group, at both ends of the clinical spectrum, show a predilection for the skin

Previously described under a variety of different names

- Hydroa vacciniforme
- Hydroa vacciniforme-like lymphoma
- Edematous scarring vasculitic panniculitis
“Hydroa vacciniforme (HV)”

- Historically defined in Western countries
- Rare photosensitivity disorder of childhood characterised by
  - Papules and vesicles on sun-exposed skin
  - Lesions evolve to crusts that heal leaving varicelliform scars
  - Symptoms usually develop in childhood and resolve during early adult life
  - No associated systemic symptoms
HYDROA VACCINIFORME-LIKE LPD: BACKGROUND

“Hydroa vacciniforme-like lymphoma”
• Name given to a syndrome clinically very similar to HV but with a more aggressive clinical course in children from:
  • East Asia
  • Latin America
  • Mexico
HYDROA VACCINIFORME-LIKE LPD: BACKGROUND

“Hydroa vacciniforme-like lymphoma”
Characterised by:

- Marked facial oedema
- Recurring vesiculopapular rashes with large ulcers and crusts
- Severe scarring and disfigurement
- Develop on sun exposed and non-sun exposed skin

Systemic symptoms usually present

- Fever
- Weight loss
- Hepatosplenomegaly
- Lymphadenopathy

Frequent association with severe mosquito bite hypersensitivity

Prognosis is often poor with a fatal outcome

- Recognised as an entity in 2008 WHO classification
- Considered separate from classical HV

Considerable clinical and pathological overlap between cases originally designated “classical HV” and “HV-like lymphoma”

Lack of reproducible morphological, immunophenotypic and molecular findings to allow the distinction of these two putative entities

Proposed that there is a spectrum of EBV-associated of T/NK-cell lymphoproliferations with HV like cutaneous manifestations:

- **Classic, self resolving HV at one end**
- **HV-like lymphoma with an aggressive clinical course at the other**

Oshima K et al, Pathol Int 2008; Cohen JI et al Annals Oncol 2009
Current approach is to include all HV-like lymphoproliferations under one heading

“Hydroa vacciniforme-like lymphoproliferative disorder (LPD)”

Recommended nomenclature used in the 2016 Update of the WHO classification
Perivascular and periadnexal infiltrate of varying density

Varied cytology of lymphocytes:
- Bland, reactive appearing
- Marked lymphocyte atypia
  - Large irregular nuclei
  - Prominent nucleoli
  - Abundant clear cytoplasm

May be associated
- Angiodestruction
- Extension into subcutaneous fat
- Spongiotic vesicles +/- ulceration

Little/no epidermotropism

Abnormal lymphocytes typically only account for 10-40% lymphocytes in infiltrate; remainder reactive
PHENOTYPE

EBV+ by definition
  • EBER+
  • LMP1 usually –

T-cell phenotype in 60-70% of cases
  • $\alpha\beta$ or $\gamma\delta$
  • Clonal TCR gene rearrangement

NK-cell phenotype in 30-40%
  • More often associated with
    • Mosquito-bite hypersensitivity
    • Prominent eosinophil infiltrate
    • Involvement of subcutaneous fat
CLINICAL CASE:

• Male aged 18 years

• History of intermittent fever for previous four years

• More recently developed heatosplenomegaly and skin lesions
**PHENOTYPE**

**Positive:**
- CD2
- cCD3
- CD7
- CD56
- EBV (EBER)

**Negative:**
- CD4
- CD5
- CD8
- TCR-βF1
TREATMENT / OUTCOME

Cases that behave aggressively:
- Severe symptoms at presentation
- Fatalities due to
  - Progression to T- or NK-cell lymphoma/leukaemia
  - Hepatic failure
  - Complication of treatment

No standard treatment
- **Multiagent chemotherapy** and **radiotherapy** offer little benefit
  - Only transient effect
  - Increase chances of sepsis or liver failure

- **Immunomodulatory therapies** may offer temporary remission / improvement of symptoms
  - Prednisolone
  - Interferon $\alpha$
  - Chloroquine
  - Thalidomide

Quintanilla-Martinez L et al, Blood 2013
2. EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE
EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE

A predominantly extranodal lymphoma characterized by

- Vascular damage and destruction
- Prominent necrosis
- Natural killer cell +/- or cytotoxic phenotype
- Epstein-Barr virus (EBV)

Designated “NK/T” (instead of “NK”), because while most cases appear to be genuine NK-cell neoplasms, some cases show a cytotoxic T-cell phenotype
EPIDEMIOLOGY

Predilection for:

- Asians
- Native American population of
  - Mexico
  - Central America
  - South America

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<thead>
<tr>
<th>Table 1. Major Lymphoma Subtypes by Geographic Region</th>
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<tbody>
<tr>
<td>Subtype</td>
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<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>PTCL-NOS</td>
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<tr>
<td>Angioimmunoblastic</td>
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<tr>
<td>ALCL, ALK positive</td>
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<tr>
<td>ALCL, ALK negative</td>
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<tr>
<td>Subcutaneous panniculitis-like</td>
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<tr>
<td>Unclassifiable T-cell</td>
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Abbreviations: PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ALCL, anaplastic large-cell lymphoma; NKTCL, natural killer/T-cell lymphoma.
Extranodal NK/T-cell Lymphoma, Nasal Type
A Report of 73 Cases at MD Anderson Cancer Center

Shaoying Li, MD,* Xiaoli Feng, MD,* Ting Li, MD,† Shuang Zhang, MD,† Zhuang Zuo, MD, PhD,* Pei Lin, MD,* Sergej Konoplev, MD, PhD,* Carlos E. Bueso-Ramos, MD, PhD,* Francisco Vega, MD, PhD,* L. Jeffrey Medeiros, MD,* and C. Cameron Yin, MD, PhD*

73 patients seen at M.D. Anderson
- 43 white (59%)
- 18 Hispanic (25%)
- 8 Asian (11%)
- 2 African American (3%)
- 2 unknown
Epidemiology otherwise similar for Western and Asian cohorts*

AGE:
Median age = 46 years (18-88 years)

SEX:
M>F, approximately 2:1

SITE OF INVOLVEMENT/PRESENTATION:
• Upper aerodigestive tract most commonly involved
  • Nasal cavity
  • Nasopharynx
  • Paranasal sinuses
  • Palate
  86% (63/73); ‘nasal type’
• Common sites of extranasal involvement:
  • Skin
  • Soft tissue
  • GIT
  • Testes
  14% (10/73); ‘extranasal type’

*figures quoted from series of Li et al, AJSP 2013
LYMPH NODE INVOLVEMENT:
• May occur as part of more widespread disease:
  • 22% (15/69) – most also with ‘nasal-type’ disease
• May present as predominantly nodal disease:

STAGE AT PRESENTATION:
• Stage I/II 65% (44/68)
• Stage IV 35% (24/68)
SYMPTOMS

Depends on organ involved

Patients with nasal involvement
• Nasal obstruction
• Sinusitis
• Ulcer
• Epistaxis
• Destructive mass o/e
• Facial swelling
MORPHOLOGY

Broad spectrum of cytology
- Small cells
- Intermediate-sized cells
- Large cells, including occasionally anaplastic morphology

Angiocentric and angiodestructive growth
- Infiltration and destruction of blood vessel walls
- Secondary necrosis
  - Not always present
  - Only in 69% (48/70) of cases in study of Li et al

Diagnosis easily overlooked
- Small biopsies
- Numerous inflammatory cells
- Necrosis
- Absence of angiocentric/angiodestructive growth
CLASSIC NK-CELL PHENOTYPE

• CD2/CD56+
• CD3- (but cytoplasmic CD3ε+ [polyclonal Ab])
• Cytotoxic molecule +

• CD4/5/7/8-
• CD16/57-
• TCR-βF1 / TCRγ –

• Epstein Barr virus present in neoplastic cells
  ➢ EBV-ISH+
  ➢ LMP1 variable

• Germline TCR

• Occasional CD56- cases described but only acceptable if EBV also present; otherwise classify as primary cutaneous peripheral T-cell lymphoma, unspecified
T-CELL PHENOTYPE / GENOTYPE:

Up to 40% (17/41) may be of T-lineage
  • Expression of T-cell associated surface markers
  • Monoclonal TCR gene rearrangement

Various T-cell markers not uncommonly expressed
  • CD2  22/23
  • CD3  68/73
  • CD4  9/31
  • CD5  7/39
  • CD7  10/25
  • CD8  11/33
  • CD30 17/40
  • CD56 62/69
  • TIA1 30/30
  • Granzyme B 19/19

(4/4 CD56 negative cases by IHC were positive by flow)
CLINICAL CASE:

• Female aged 47 years
• Ulcerating lesion in nasal cavity
• ‘Skin lesions’ on right upper arm
Cytoplasmic CD3 (CD3ε)
Other pan-T-cell antigens negative

CD5

CD7
Negative for CD4 and CD8

CD4

CD8
Cytotoxic molecules:
- TIA-1+
- Granzyme B+
- Perforin+
CLINICAL CASE:

- Male aged 66 years
- Area of erythema and ulceration on right shin

• ENKTCL can occasional show epidermotropism
  • D/Dx with other epidermotropic CTCL
• ENKTCL can involve subcutaneous fat
• D/Dx SPTCL, GDTCL
Angiolytic growth pattern common
TREATMENT / OUTCOME

An aggressive disease:

• Median overall survival 4.2 years (13-42 months in literature)
• 5-year-overall survival 46% (20-65% in literature)

• Nasal disease 5-year OS 5.01 years
• Extranasal disease 5-year OS 0.55 years

• Stage I/II disease benefits from combined chemoradiotherapy
• Stage IV disease does badly regardless of treatment modality

Li S et al, Am J Surg Path 2013
D/Dx HV-LIKE LPD FROM ENKTCL

There may be significant overlap between HV-like LPD, ENKTCL and other lymphomas, e.g.

- Angiocentricity and angiodestruction
- Infiltration of subcutaneous fat
- T-cell phenotype in some ENKTCL and HV-like LPD (including γδ phenotype)
- Demonstration of EBV in neoplastic cells is central to diagnosis
  - Requires in situ hybridization (EBERs)

HV-like LPD and ENKTCL share many pathological features and separation often depends on clinical features;

- **HV-like LPD typically**
  - Younger age group
  - More protracted course; recurring papules and vesicles
- **ENKTCL characterized by**
  - Progressive disease
  - Destructive masses