Case 3
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Case 3-History
- Newly discovered ascites in 73 y.o.
  Greek man admitted for an upper gastro-intestinal bleed

Additional clinical information
- Other signs & symptoms
  - lower extremity edema, dyspnea and non-productive cough
- Past medical history
  - diabetes mellitus
  - hypertension
  - renal insufficiency
  - atrial fibrillation
- Exam
  - ascites in the absence of palpable adenopathy or hepatosplenomegaly

Laboratory data
- Normal
  - complete blood count
  - liver function tests
  - lactate dehydrogenase
  - serum protein
- HIV-negative
- Hepatitis B and C virus-negative
- Normal serum Ig levels, no monoclonal peak
- CT scans of the abdomen and thorax
  - non-cirrhotic liver
  - No lymphadenopathy or organomegaly

Smear-Pap stain- 100X
Smear-Pap stain-200X
Clinical history

- CHOP + continuous daily oral valganciclovir started
- Tolerated chemotherapy, had a satisfactory clinical response and returned home on daily valganciclovir
- Shortly thereafter, returned to the hospital with recurrent ascites and non-obstructive ileus
  - A 6 liter paracentesis was performed = persistent PEL
  - Small right-sided effusion also noted
- Following a prolonged admission, patient discharged with a tentative plan of a third cycle of CHOP
- Within weeks of discharge, was readmitted with acute respiratory failure
  - Bilateral pleural effusions and a large pericardial effusion
  - Cytology from both the pericardial and pleural fluids: PEL
- Supportive care strategy adopted
  - died within 5 months of the initial diagnosis of PEL

Primary Effusion Lymphoma (PEL)

- According to WHO 2008
  - An entity on its own in the “Mature B-cell neoplasms” category
  - distinct from diffuse large B-cell lymphoma, NOS
- Definition
  - Distinct clinicopathologic entity defined as large B-cell neoplasm usually presenting as serous effusions without detectable masses
  - Universally associated with HHV8
  - Most often occurs in setting of immunodeficiency
  - Some cases can 2arily develop solid tumors in adjacent structures, such as pleura
  - Rare HHV8+ lymphomas indistinguishable from PEL present as solid tumors=extracavitary PEL

Epidemiology

- Majority in young or middle-aged homosexuals or bisexual males with HIV+
  - Mostly in the fourth decade of life
  - Usually severely immunosuppressed
  - T cell count < 100/mm3
  - Prior manifestations of AIDS
- Has also been reported
  - in women
  - in other severe immunodeficiency states
  - in recipients of solid organ transplants
  - in absence of HIV
  - Usually in elderly patients (men and women)
  - Mostly in areas with high prevalence of HHV8 infection (Mediterranean)

Epidemiology-2

- HIV- neg. patients with PEL may have underlying immunodeficiency due to
  - Advanced age
  - Cirrhosis
  - Cancer
  - Transplantation
  - Birth in areas of high prevalence of HHV8 infection
    - Mediterranean region

Sites of involvement

- Most common sites
  - Pleural
  - Pericardial
  - Peritoneal
- Typically, only 1 body cavity is involved
- Extracavitary PEL
  - Extranodal sites
    - GI, skin, lung, CNS
  - Lymph nodes
PEL: clinical features

- Typically present with effusions in absence of lymphadenopathy or organomegaly
- 1/2 have pre-existent or develop Kaposi sarcoma
- Occasionally, also have multicentric Castleman disease

Morphology

- Range of appearances from
  - Large immunoblastic or plasmablastic cells, to
  - Anaplastic morphology
- Large, round to irregular nuclei
- Prominent nucleoli
- Abundant cytoplasm
  - Can be deeply basophilic with vacuoles
- Perinuclear hof (plasmacytoid differentiation) may be seen
- Occasional cells resemble Reed-Sternberg cells

Immunohistochemistry

- Usually CD45+
- Lack:
  - Pan-B markers such as CD19, CD20 and CD79a
  - surface and cytoplasmic Ig
  - BCL6 (usually)
- Often positive for activation and plasma cell related markers and other non-lineage-associated antigens
  - CD30, CD38, CD138, HLA-DR, CD77
  - EMA
- Lack T/NK-cell Ag
  - But aberrant expression of T-cell markers may occur
- Nuclei: positive for HHV8-associated latent protein LANA
- EBV
  - LMP1: - by IHC
  - but usually + by EBER in situ hybridization

PEL-Genetics I

- Ig genes are clonally arranged and hypermutated
- Some cases with T-cell receptor gene rearrangement (genotypic infidelity)
- No recurrent chromosomal abnormalities reported
  - Often gains in chromo 12 and X
- HHV8 genome (½ cases) with potential oncogenes
  - Viral cyclin homologue
  - Viral IL-6
  - Gene homologous to G protein-coupled receptor family of proteins
- In AIDS-related PEL, distinct features of both
  - plasma cells, and
  - EBV-transformed lymphoblastoid cell lines

PEL-Genetics II

- Tumors cells usually co-infected with EBV, is a γ herpesvirus closely related to HHV8
- Genetic profile of late postgerminal center B cell in most cases
Treatment options

- CHOP-like regimens: considered 1st line therapy
  - Sub-optimal as most patients do not respond
- HAART alone not useful to control HHV-8
- Anti-viral therapy

Prognosis

- Extremely unfavourable clinical outlook
  - Median survival: <6 months
- Only few long-term survivors, even with high-dose chemotherapy and autologous stem cell reinfusion
- Rare cases have responded to chemotherapy and/or immune modulation

PEL: differential diagnosis I

- Pyothorax-associated lymphoma
  - Arises in pleural cavity following long-standing inflammation
    - Mine workers, artificial pneumothorax, tuberculous pleuritis
  - B cells with plasmacytoid differentiation
  - Usually associated with a tumor mass localized in body cavity
  - Association with EBV
  - BUT negative for HHV8
- Rare cases of Burkitt lymphoma, even with no tumor masses
  - Are morphologically and immunophenotypically distinctive
  - Have C-MYC rearrangement
  - Not associated with HHV8

PEL: differential diagnosis II

- Plasmablastic lymphoma
  - May arise in patients with HHV8 and multicentric Castleman’s disease
  - Usually involve the spleen or lymph nodes
  - EBV-negative
  - Often + for CD20 and cytoplasmic Ig, which is always IgM/Lambda restricted
- HHV8-negative effusion-based lymphoma
  - Also called HHV8-unrelated PEL-like lymphoma
  - Associated with chronic liver disease, most due to HCV
  - Most involve peritoneum and pleura
  - Large cell morphology: 80% cases
  - B-cell immunophenotype: 90% of cases

PEL-Pathogenesis

- Neoplastic cells: HHV8+ in ALL cases
- Most cases also co-infected with EBV
  - Has a restricted gene expression
  - may not be required for pathogenesis
- HHV8 encodes >10 homologues to cellular genes providing proliferative and anti-apoptotic signals

Pathogenesis

- HHV8 sequences are present in much greater numbers in PEL than in Kaposi sarcoma
  - Viral particles (100- to 115-nm capsids with central cores) can be readily identified
    - by EM: within the nucleus and cytoplasm of the neoplastic cells
    - by IHC: using Ab to LANA (ORF-73)
- Risk group for HIV-related PEL similar to KS
  - KS lesions are present in 1/3 of PEL cases
- Seropositivity for HHV8 much higher than the incidence of HHV8-related disorders
  - Indication that other factors, including immunosuppression, are involved in the pathogenesis
- PEL in the HIV+
  - Invariably associated with EBV, usually monoclonal
  - But EBV has restricted gene expression, not required for pathogenesis
HHV8

• Member of gamma herpes virus family, which also includes EBV
• Linear double-stranded DNA virus
• Not ubiquitous, but has endemic areas of infection
  – Sub-Saharan Africa: seroprevalence = 50-70%
  – Mediterranean region: seroprevalence = 20-30%
    (In contrast, in North America: seroprevalence = 1-3%)
• Mode of transmission documented
  – Mother to child, sexual contact, household, needle sharing, blood transfusion, organ transplantation
  – Because human epithelial cells and keratinocytes support HHV8 infection and replication, mucosal tissues are likely most important site of infection

HHV8-associated lymphoproliferative disorders

• PEL- in the absence of tumor masses
• “Solid” lymphomas with serous effusions
  – Prior to the development of PEL
  – Following the resolution of PEL
• “Solid” lymphomas without serous effusions
  – Extracavitary (extranodal) tissue based
  – Extracavitary (lymph node) based
• Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
• Germinotrophic lymphoproliferative disorders


HHV8-associated lesions

• Kaposi sarcoma
• Primary effusion lymphoma
  – Multicentric Castleman disease
    – Nearly 100% of cases with HHV+ patients are HHV8+
    – A subset of cases in HIV- patients are HHV8+
  – Plasmablastic proliferations arising in the setting of multicentric Castleman disease
    – In plasmablastic Castleman disease: HHV8 localized in plasmablasts scattered in expanded follicle mantles
    – In plasmablastic microlymphoma: plasmablasts proliferate to replace whole follicles
    – Frank plasmablastic lymphoma: plasmablasts grow diffusely
  – Germinotrophic lymphoproliferative disorders
    – Plasmablasts co-infected by HHV8+ and EBV+
    – Histologic features similar to plasmablastic microlymphoma
    – Affects HIV- patients
    – Present with lymphadenopathy without systemic symptoms
    – Good outcome
• HHV8-positive lymphomas account for ~3% of AIDS-related NHLs, and < 1% non-AIDS NHLs

Extracavitary HHV8 lymphoma

• Other names: extracavitary PEL or solid immunoblastic/plasmablastic lymphoma
• HHV8+ lymphoma with morphology and immunophenotype similar to those of PEL
• Can present as solid tumor masses in absence of an effusion
• May occur in
  – GI tract
  – other extranodal sites
  – Lung
  – CNS
  – skin

Extracavitary HHV8 lymphoma

• May express B-cell antigens or Ig in up to 25% of cases
  – More often than the neoplastic cells in PEL
• HIV+ patients who develop solid PEL
  – May be less immunosuppressed
  – Have a better survival than those with PEL

History-KS

• 1872: Kaposi sarcoma first described by Hungarian dermatologist Moritz Kaposi (1837-1902)
  – Classic type in elderly men, particularly of Mediterranean, Eastern European, or Jewish heritage
  – Born Moritz Kohn in Kaposvar, Hungary
  – In 1871, officially changed his last name to Kaposi (after his birthplace)
  – Acknowledged during his lifetime as one of the great masters of Vienna School of Dermatology, superb clinician and renowned teacher
History-KS
• 1950s: a high occurrence of endemic KS reported in equatorial Africa
• 1960s: KS emerged among immunosuppressed patients after solid organ transplantation
• 1980s: tremendous increase in incidence of KS
  – Due to emergence of AIDS

History-PEL & HHV8
• 1989: PEL first described by Knowles et al
• 1994: HHV8: first characterized by Chang et al in HIV+ patients with Kaposi sarcoma (Kaposi’s sarcoma-associated herpes virus KSHV)
  – Husband & wife team
    - Yuan Chan: pathologist
    - Patrick Moore: public health epidemiologist
• 1995: Ceserman et al report presence of HHV8 in AIDS-related “body cavity-based lymphoma”
• 1995: Soulier et al report presence of HHV8 in multicentric Castleman’s disease
• 1996: Nador RG et al coined the name Primary Effusion Lymphoma (to distinguish from "secondary lymphomatous effusions")
• 2001: PEL is distinct entity in WHO classification

PEL-New developments in therapy
• Antiviral intra-cavitary therapy
  – Can presumably reach higher concentrations in critical areas to have proapoptotic effect on lymphoma cells
  – Such levels cannot be achieved safely when administered systemically
  – Duration of responses: 5-15 months
  – May be reasonable therapy in frail, elderly patients or when refractory to conventional chemotherapy

PEL-New developments in spectrum of disease
• Sites of involvements in PEL
  – Rare cases of PEL can arise in spaces without a mesothelial lining
    – in subarachnoid space
    – In artificial cavity formed adjacent to the capsule to the capsule of silicone breast implant
  – Extracavitary PEL: forming solid masses in lymph nodes and extranodal sites

New developments in spectrum of disease associated with HHV8
• Reports of different morphology of HHV8-associated lymphoma
  – Hodgkin-lymphoma like large B-cell lymphoma
    – 1 case in HIV- negative patient
    – Presence of large, bizarre cells in a reactive background of interfollicular regions
    – Also, some hallmark-like cells
    – But CD45+, CD15-, CD30-, EMA+
  – Intravascular large B-cell lymphoma

Conclusion: The future
• Aim to better understand
  – Spectrum of pathologic and clinical manifestations
  – Pathogenesis
  – Treatment options: need controlled clinical trials
    – Better antiviral therapy
    – Monoclonal antibody therapy
      – anti-CD20
    – mTOR inhibitors
    – Angiogenesis inhibitors (INF-alpha)
    – Have shown efficacy against PEL in culture
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