AETC AIDS Education & Training Center Program Mountain West

HIV Sepsis Imposters

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Project ECHO®

Disclosures

Merck: Adjudicated cases for HIV diagnostic test development

All relevant financial relationships have been mitigated.

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Disclaimer

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Case 1

Case 1

- 48 yo HIV+ man diagnosed in May 2016 with a CD4 of 47. Started on ART and rapidly suppressed but then presented in June 2016 with fatigue, dyspnea, night sweats and headache for weeks.
- On presentation he was pale and ill appearing with a T of 38.2, HR 138, BP 117/63, RR 18. No mention of adenopathy on exam.
- Hct 17, WBC 5.5, plts 32. CXR normal, Head CT normal
- Empirically treated with meropenem, vancomycin, acyclovir and ART
- BCs, UCs, AFB and fungal BCs negative, CrAg negative, CSF studies (CrAg, CMV, EBV, HSV, VZV) negative, urine Histo Ag negative, serum Parvovirus negative

Case 1

What do you want next?

CT of CAP: Massive splenomegaly with diffuse axillary, retroperitoneal and pelvic adenopathy

HHV-8 level: 2.3 million

L axillary lymphnode: HHV-8 associated plasmablastic proliferation. Although the morphology is not typical for MCD, it is likely that this process evolved from MCD

He was treated with weekly rituximab for 4 doses.
He then developed KS and bilateral pleural effusions that prompted Rx with liposomal Doxorubicin and Val-ganciclovir for persistently + HHV-8 levels (29-580K)
He died unexpectedly months later

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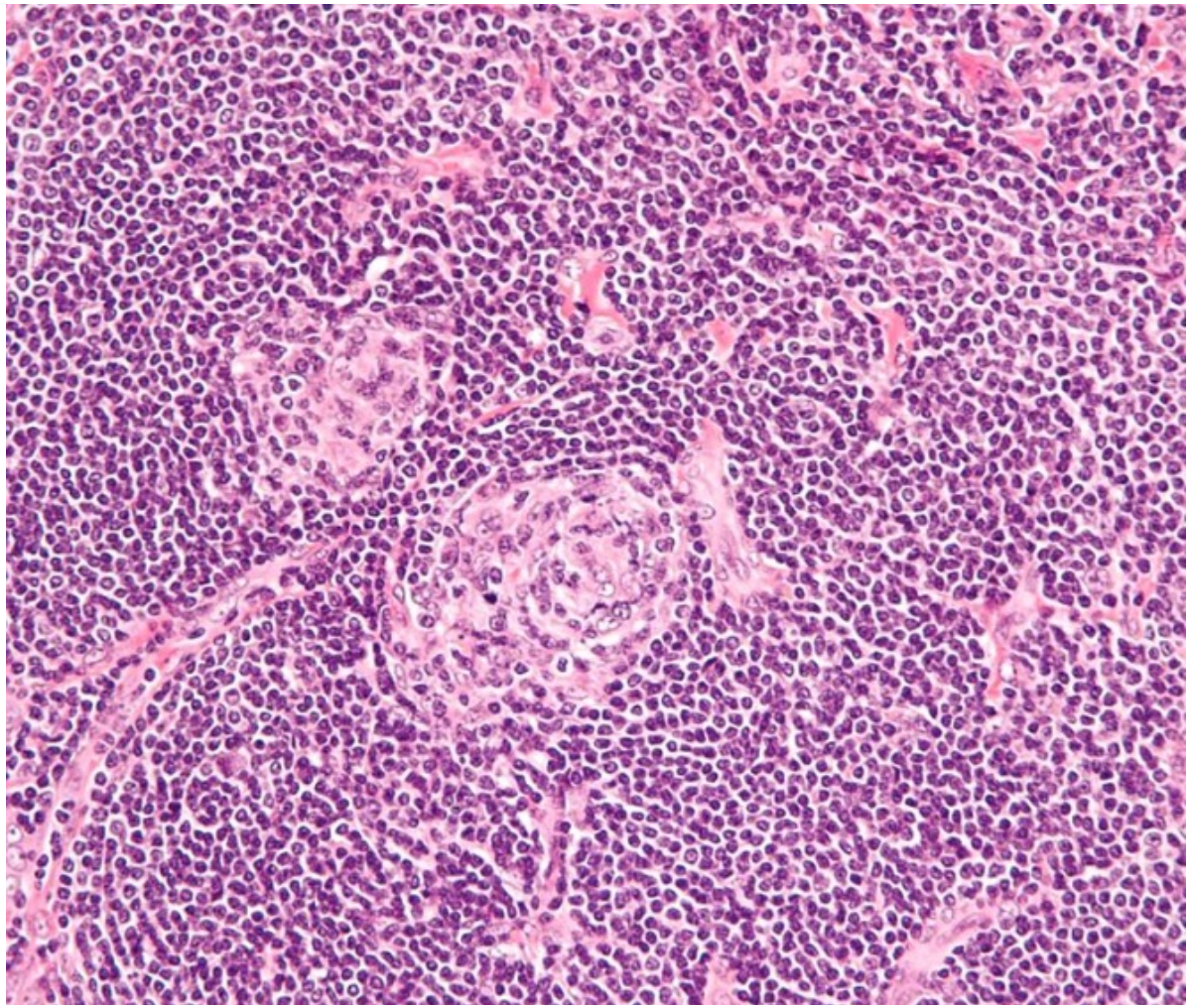
KSHV Associated Multi-centric Castleman's Disease (MCD)

- MCD: A lymphoproliferative disorder affecting B-cells and plasma cells
- Clinically
  - Episodic flares of inflammatory symptoms including fevers, night sweats, fatigue, cachexia, edema with tender lymphadenopathy and/or hepatosplenomegaly. Other involved organ systems: lung and GI.
  - Can evolve into large B-cell lymphoma
  - KS is present in 70% of patients
  - Laboratory findings: cytopenias, low albumin, hyponatremia, elevated CRP
  - Flares typically associated with high plasma KSHV levels
  - Without therapy the condition is generally fatal

KSHV Associated Multi-centric Castleman's Disease (MCD)

- Diagnosis: based on lymph node pathology
  - Three histologic categories
    - Plasma cell
    - Hyaline vascular
    - Mixed variants
  - Vascular hyperplasia
  - Expansion of KSHV infected and reactive plasmacytoid B lymphocytes
  - Concurrent KS in the same lymph node often present



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KSHV Associated Multi-centric Castleman's Disease (MCD)

- Pathogenesis
  - Several KSHV genes that are expressed in the lytic phase of infection (vFLIP, vGPCR, Kaposin B) act through activation of transcriptional factor NF-kB to enhance expression of human IL-6, and IL-10
  - Viral homologue of IL-6, vIL-6, is also thought to play a role

KSHV Associated Multi-centric Castleman's Disease (MCD)

- Treatment
  - Anti-retroviral therapy
  - Rituximab (375 mg/M^2) weekly for 4 weeks
    - Targets KSVH infected cells expressing CD-20
    - Eliminates reactive B-cells thereby depriving KSHV cells of cytokine signals
  - Chemotherapy (typically etoposide or liposomal-doxorubicin)
  - Val-ganciclovir (anti-KSHV effect) plus high dose AZT (phosphorylated by viral kinases – leading to selective toxicity of infected cells) also effective
  - Siltuximab (anti-human-IL-6, Not vIL-6) and tocilizumab (anti-IL-6 receptor) are under investigation

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KSHV Associated Multi-centric Castleman's Disease (MCD)

- Recent Systematic Review of Treatment for MCD (Rokx, Netherlands J Med 2015)
- 19 studies, 666 patients, 450 with HIV
- Patient characteristics:
  - ART coverage 65%, suppressed 41%
  - Median CD4 221 (148-398)
  - Plasma HHV-8 pcr +: 99.7%
  - KS was present in 56%
- Mortality:
  - Overall: 25%
  - Treatment with chemotherapy alone: 37%
  - Treatment with rituximab (with or w/o chemotherapy): 10%
  - Anti IL-6 therapy (mostly used in HIV uninfected persons): 8%
- Other outcomes
  - Progression of KS in 13% (mostly those treated with rituximab alone)
  - Lymphoma developed in 15%
  - Three studies on 149 patients with MCD reported that 34% developed HLH

Gerard Blood 2010, Dosser CID 2013, Guihot Eur Resp J 2005)

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Case 2

Case 2

- 47 yo HIV+ man AIDS (CD4 nadir 10) with h/o KS, MCD – treated with 4 cycles of rituximab and doxil (2011), cerebral toxoplasmosis (2009) now presents with 3 days of fever, myalgia, headache and fatigue. Current CD4 > 400, HIV RNA 72 copies/mL. ART: abacavir, etravirine and raltegravir.
- Similar presentations 2013 and 2014 that resolved without specific therapy. Notably, then had HHV-8 levels of 35,000 and 7000 respectively.
- Ill appearing man, T 38.9, HR 150 and BP 70/p. No tender adenopathy or HSM, KS lesions on feet.
- WBC 7.3, Hct 43, Plts 47, creat 1.2, LFTs normal but for albumin of 2.9.
- CXR normal, CT head normal.

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Case 2

- Admitted to ICU and treated with IV fluids and abx (vancomycin and meropenem)
- CSF formula benign, CSF viral, fungal and bacterial studies negative, BCs negative
- What is going on and what tests do you want?

- CRP 170
- HHV-8 1.2 million copies
- IL-6 level 93.5

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KSHV Inflammatory Cytokine Syndrome (KICS)

- Lytic HHV-8 expression leads to the expression of viral-IL-6 and other genes that induce expression of human-IL-6, suppression of T-regulatory cells and activation of macrophages and PMNs
- Clinical Presentation and Diagnosis/Working Case Definition:
  - At least 2 clinical manifestations (see 1- a,b,c below) + 2 + 3 + 4

Category	Details
1. Clinical manifestations	
a. Symptoms	Fever, fatigue, edema, cachexia, respiratory symptoms, GI symptoms, arthralgia and myalgia, AMS, neuropathy with or without pain
b. Labs	Anemia, low plts, low Na, low albumin
c. Radiographic	Lymphadenopathy, HSM, body cavity effusions
2. Systemic inflammation	CRP $\geq$ 3 mg/dL
3. KSVH viral activity	Plasma HHV-8 > 1000 copies/mL or PBMCs > 100 copies of HHV-8
4. No MCD	No evidence of MCD on histopathology

KSHV Inflammatory Cytokine Syndrome (KICS)

	KICS	MCD	KS-IRIS
Definition	MCD without pathologic confirmation	Lymphoproliferative d/o, systemic inflammation, high KSHV viremia, Typical histopathology	New and inflamed KS lesions after starting ART
Histopathology		Lymph node: KSHV infected, polyclonal plasmacytoid cells	KS with atypical inflammatory component t
KSHV viremia	High	High	Low
Temporal assoc ART	No	No	Yes
Cytokines	High hIL-6, vIL-6 & IL-10	High hIL-6, vIL-6 & IL-10	?
HIV viremia	High	Low	Low
CD4 count	< 100	> 200	On the rise

KSHV Inflammatory Cytokine Syndrome (KICS)

Treatment and Outcomes

- No clear treatment regimens. Generally, use same therapies as for MCD.
- Rituximab monotherapy:
  - 92% resolved symptoms at 60 days
  - But 1/3 developed worsening KS (are B-cells important for controlling KS?)
- Rituximab + liposomal-doxorubicin
  - Event-free survival at 1 year: 82%
  - Only 1/17 patients had progression of KS

Cantos Open Forum ID 2017; Gerard J Clin Oncol 2007

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Case 2 - continued

- Diagnosed with KICS
- Treated with liposomal doxorubicin, rituximab, prednisone and val-ganciclovir
- Discharged in 7 days
- Two more cycles of liposomal doxorubicin and rituximab as an outpatient
- No further recurrences

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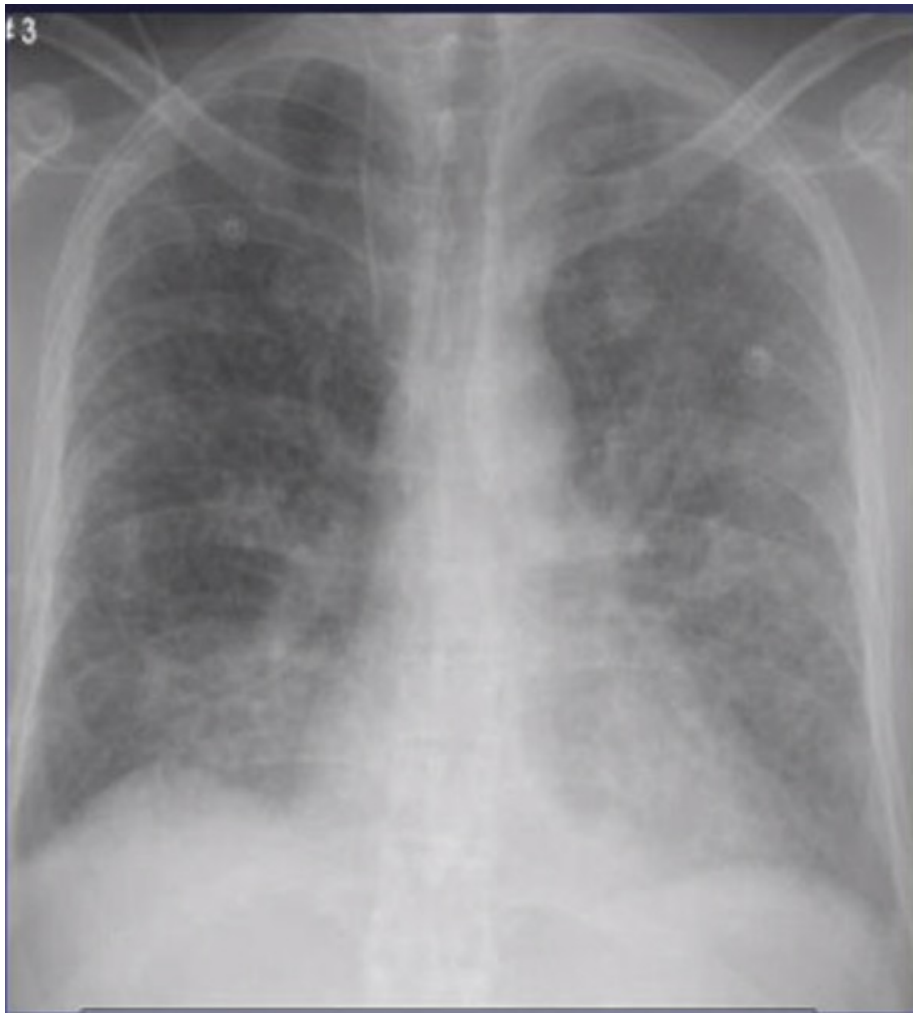
Case 3

- A 24 yo MSM moved to Seattle from southern Indiana where he worked as a laborer on free-range chicken farm shoveling manure.
- He fell ill on the bus ride west and arrived at the HMC ED with fever (39), cough, dyspnea, LE edema and headache. Exam revealed an acutely ill-appearing young man with a BP of 90/60, HR 126, RR 30, mild meningismus, fine rales at the lung bases and a tender LUQ.
- CXR is shown



Case 3

- Hgb: 8, Plts 90k, WBC 1.2
- HIV 4th generation test is + but confirmatory Ab testing is negative
- What tests do you want next?
- HIVRNA is 1,200,000 copies
- Urinary histoplasma Ag is ++
- He is started on amphotericin and a week later on bictegravir-TAF-FTC but he remains febrile and now his Hgb is 6, Plts are 80K and WBC is 0.8
- What tests do you want now?

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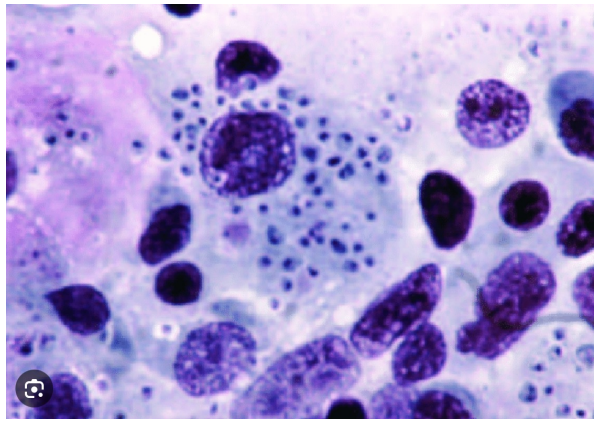
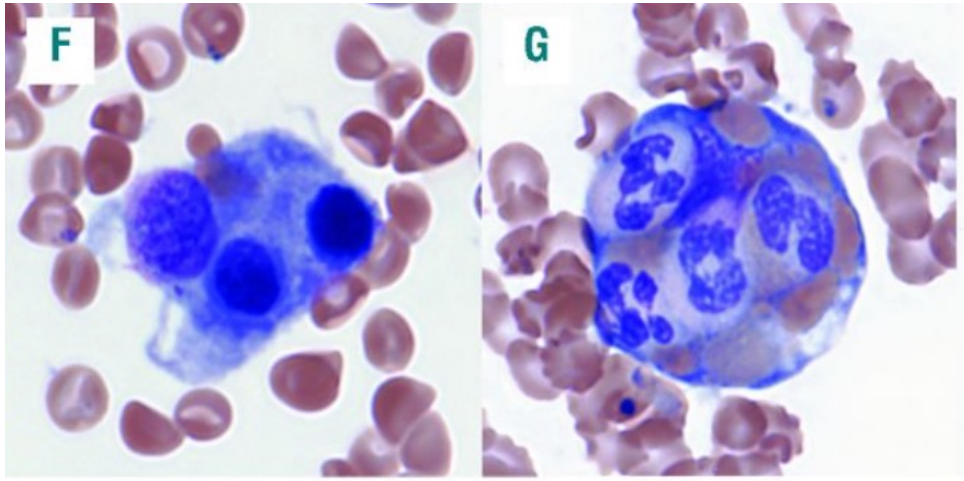
Case 3

- Ferritin is 15,000
- Triglycerides are 350
- sCD25 is 3500 (send out test)
- BM biopsy shows this



But also this:



He is diagnosed with primary HIV, disseminated Histoplasmosis and Hemophagocytic Lymphohistiocytosis (HLH)

Hemophagocytic Lymphohistiocytosis (HLH)

- Definition: Upregulated and hyperactive T-lymphocytes and macrophages that lead to hematopoetic cell phagocytosis and cytokine release
- Two forms: Primary and Secondary
  - Primary: genetic disorders: genes involved in perforin function (*PRF*), granule secretion (*UNC13D*), intracellular trafficking (*STX11*), signal transduction of T and NK cells (*SAP*), lysosomal trafficking (*LYST1*) and granule exocytosis (*RAB27a*)
  - Secondary: triggered by infections, malignancies and autoimmune d/o

Hemophagocytic Lymphohistiocytosis (HLH)

Clinical Presentation and Diagnosis

- Genetic diagnosis OR
- Clinical and Laboratory Criteria: must have 5/9
  - Fever
  - Splenomegaly
  - Cytopenias (affect 2 of 3 lines): Hgb < 9, Plts < 100, PMN < 100
  - Hypertriglyceridemia or hypofibrinogenemia: TG > 265 or Fibrinogen < 150
  - Hemophagocytosis on bx of BM, lymph node, spleen or liver
  - Low or absent NK activity
  - Ferritin > 500
  - Soluble CD25 (IL-2 receptor) > 2400
  - Elevated CXCL9

Henter Pediatric Blood Cancer 2007

Hemophagocytic Lymphohistiocytosis (HLH)

Review of 81 Patients with HIV & HLH from 70 Articles

- Median age: 40; 78% male
- Clinical presentation ranged from acute illness to chronic wasting syndrome (median time from symptom onset to diagnosis:18 days (range 1-330)
- Median time from HIV diagnosis → HLH: 1 year (range 0.3-6)
- On ART at the time of HLH dx: 69% (35/53)
- HLH was presenting symptom leading to HIV dx: 35% (28/81): 1/3 of these had primary HIV
- HIV suppressed at HLH dx: 12% (10/81)

Hemophagocytic Lymphohistiocytosis (HLH)

Review of 81 Patients with HIV & HLH from 70 Articles

Trigger	N (total n=81)	% Cured	% Died
Acute HIV	9	100%	0
IRIS	15	40%	60%
HIV only (without primary HIV)	12	67%	33%
Viral infections *EBV, HHV-8, CMV, HSV, HBV, Parvo B19	43	58%	42%
Invasive fungal infection (**Histoplasma**, Cryptococcus, Aspergillus, PJP, Penicillium)	20	75%	25%
Bacterial infection (CAP, MTB, MAC, Syphilis, C diff, Bartonella, Ehrlichia, bacteremia)	12	58%	42%
Parasitic infection (Toxoplasma, malaria, Leishmania)	4	75%	25%
Malignancy (Lymphoma, Myeloma)	8	25%	75%

Hemophagocytic Lymphohistiocytosis (HLH)

Review of 81 Patients with HIV & HLH from 70 Articles

- Overall mortality: 40%
- 60% (49/81) received HLH-directed Rx (mix of steroids, IVIG, chemotherapy (etoposide), anakinra, cyclosporin). 50% of these patients died
- Those with IRIS and cancer fared worse, mortality 60% and 75%
- Those with invasive fungal infections did better; mortality 25%
- In general, when the triggering illnesses was treated, patients did well with or without HLH directed treatment
- After cure only 3 patients relapsed

HIV Sepsis Imposters: MCD, KICS, HLH

- Uncommon inflammatory disorders that occur in HIV+ patients
- Highly associated with replicating HHV-8 and HHV-8 associated cancers (MCD & KICS) or other infectious and malignancy triggers (HLH)
- Clinical presentation:
  - MCD & KICS: moderately to severely ill with high fever, sweats, edema, adenopathy, hepatosplenomegaly, organ dysfunction, cytopenias, hyponatremia, hypoalbuminemia and elevated HHV-8 levels
  - HLH: cytopenias, phagocytosis, fever, HSM, elevated CD25, ferritin, CXCL9, reduced NK activity
- Pathogenesis:
  - MCD & KICS: HHV8-→ elevated IL-6 and IL-10 levels (and vIL-6)
  - HLH: triggers of macrophage activation
- Treatment
  - MCD & KICS: ART + rituximab + liposomal doxorubicin (if KS or organ dysfunction).
  - HLH: treat the trigger +/- HLH directed therapy (e.g. etoposide & steroids)

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