Infections in Cancer Patients

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Disclosures of Financial Relationships with Relevant Commercial Interests

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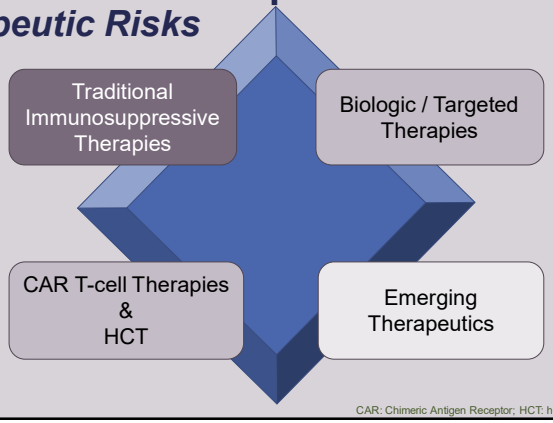
Objectives

- Review testable complications in relevant immunocompromised hosts
- Broadly categorized, this includes
  - Risks of underlying diseases and applied chemo-, immunomodulatory and cellular therapies
  - Recognition of breakthrough infections
  - Recognition of specific clinical “syndromes”

Fundamental Concepts
Risk of Underlying Disease

- Important immune deficits associated with underlying disease
- Examples include
  - Acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS) – qualitative and quantitative neutropenia
  - Lymphomas – functional asplenia
  - Chronic lymphocytic leukemia (CLL) – hypogammaglobulinemia, complement deficiencies, neutrophil/monocyte defects
  - Multiple myeloma – hypogammaglobulinemia
  - Aplastic anemia – severe, prolonged neutropenia

Fundamental Concepts
Therapeutic Risks



CAR: Chimeric Antigen Receptor; HCT: hematopoietic cell transplant

Fundamental Concepts
Therapeutic Risks

- Drugs that impact neutrophils
  - Cytotoxic chemotherapy (e.g., anthracycline, cyclophosphamide)
    - Infectious risks greatest when prolonged (> 7 days) and profound (< 500 cells/mm3) neutropenia
    - Severe bacterial and fungal infections

Fundamental Concepts
Therapeutic Risks

- Drugs that impact T cells
  - Purine analogs (fludaribine, cladribine, clofarabine) and temozolomide
    - Infections associated with
      - Herpesviruses (e.g., CMV, HSV, VZV)
      - Intracellular and other less common bacteria (e.g., Mycobacteria, Nocardia)
      - Fungi (e.g., PJP, Aspergillus)

CMV: Cytomegalovirus, HSV: herpes simplex virus; VZV: varicella zoster virus; PJP: *Pneumocystis jirovecii* pneumonia

Biologic / Targeted Therapies
****Online Lecture - Immunomodulatory Agents: What Can Be Tested****

Immunomodulatory Therapy	Examples	Board Buzz - Infection Risk
CD20 inhibitors	Rituximab, obintuzumab	Hepatitis B reactivation, impaired vaccine response, hypogammaglobulinemia, rare JCV PML
CD52 inhibitors	Alemtuzumab	PJP, CMV, HSV/VZV, other invasive fungal and opportunistic infections
TNF-alpha inhibitors	Infliximab, adalimumab	Tuberculosis, endemic fungi, other intracellular pathogens
Janus kinase inhibitors	Tofacitinib, ruxolitinib	Herpes zoster, TB/NTM, other opportunists
Interleukin-6 inhibitors	Tocilizumab, sarilumab	Severe infections, masked infectious signs/symptoms – normal CRP, GI perforation
Complement inhibitors	Eculizumab, ravulizumab	Severe/disseminated *Neisseria meningitis*, Gonococcal infections, other encapsulated bacteremia (e.g., Pneumococcus, *H. influenzae*)
Checkpoint inhibitors	Pembrolizumab, nivolumab, ipilimumab	PJP when treated for iRAEs and no prophylaxis, mimics from iRAEs (e.g.,pneumonitis, colitis)
Bruton's tyrosine kinase inhibitors	Ibrutinib, acalabrutinib	Invasive fungal infections (e.g., aspergillosis, cryptococcosis), including CNS involvement/dissemination

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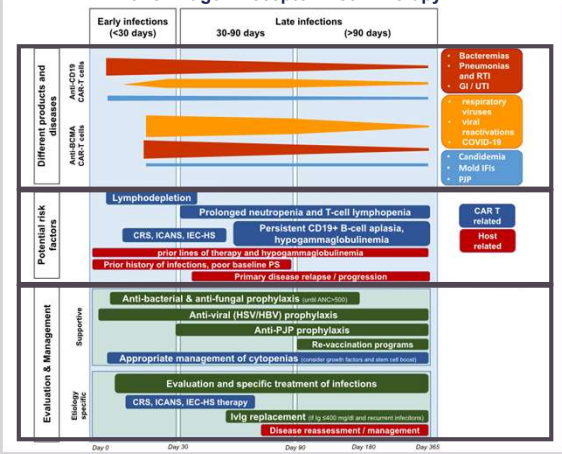
Question #1

- 61-year-old patient with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) is now day +2 following CD-19-directed CAR T-cell therapy following Axicabtagene ciloleucel and received lymphodepleting chemotherapy with fludarabine and cyclophosphamide. Prophylaxis includes valacyclovir, levofloxacin, fluconazole, and SMX-TMP.
- He develops fever to 102, hypotension (90/60) requiring low-dose norepinephrine, tachycardia (HR 120s), and hypoxia (SaO2 90%). Blood cultures (peripheral and central line), urinalysis, and urine culture are sent. CXR and CT chest show mild bilateral ground-glass opacities and small pleural effusions.
- Labs: WBC 0.5 (ANC 0), CRP 4.0->10mg/dL, ferritin 200->2000 ng/mL. Remaining labs are stable.

Which of the following is the most appropriate management?

A. Modify antimicrobials: levofloxacin → IV cefepime and administer tocilizumab
B. Modify antimicrobials: levofloxacin → IV cefepime + vancomycin and administer tocilizumab
C. Modify antimicrobials: fluconazole → IV liposomal amphotericin B
D. Modify antimicrobials: valacyclovir→ IV ganciclovir
E. Administer tocilizumab x 1 dose

Chimeric Antigen Receptor T-cell Therapy



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From: Shahid Z, et al. Transplant Cell Ther. 2024 Oct;30(10):955.

Chimeric Antigen Receptor (CAR) T-cell Therapy

Variable	Cytokine Release Syndrome (CRS)	Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)
Definition	**Supraphysiologic response** after immune therapy with activation or engagement of endogenous or infused T cells and/or other immune effector cells	**Pathologic process involving the CNS** after immune therapy with activation or engagement of endogenous or infused T cells and/or other immune effector cells
Typical Onset	Early (2-3 days post-infusion)	Biphasic: early (4-10 days, overlaps with CRS), late (up to 1 month)
Incidence (range)	57-93%	20-70%
Typical Duration	7-8 days	Typically self-limited, most often 5-17 days
Typical signs/ Symptoms	**Fever (cardinal),** hypotension, hypoxia (capillary leak), may have end-organ dysfunction	Aphasia, altered consciousness, impaired cognitive skills, motor weakness, seizures, cerebral edema
First-Line Management	Supportive care (rule out infection, empiric antimicrobials + CRS directed therapies including **tocilizumab +/- corticosteroids** based on grading)	Supportive care + corticosteroids + seizures medications ***Tocilizumab does not resolve ICANS, may worsen it**

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Lee DW et al, Biol Blood Marrow Transplant. 2019;25(4):625.
Naidoo J et al. J Clin Oncol. 2021;39(35):3978. PMID: 34724386.

A Brief Primer On Consensus Grading, NOT for Memorization But For Context…

CRS Grading	Relevant Variables	Management
Grade 1	**Fever: temperature ≥ 38°C** Hypotension: none Hypoxia: none	Supportive care including consideration of broad-spectrum antibiotics, if persistent proceed to grade 2
Grade 2	**Fever: temperature ≥ 38°C** *plus* Hypotension: not requiring vasopressors *and/or* Hypoxia: requiring low-flow nasal cannula	Supportive care as above + tocilizumab +/- corticosteroids
Grade 3	**Fever: temperature ≥ 38°C** *plus* Hypotension: requiring vasopressors *and/or* Hypoxia: requiring high -flow nasal cannula, facemask, non-rebreather mask, or Venturi mask	Supportive care as above + tocilizumab +corticosteroids, admission to ICU
Grade 4	**Fever: temperature ≥ 38°C** *plus* Hypotension: requiring multiple vasopressors *and/or* Hypoxia: requiring positive pressure	Supportive care as above + tocilizumab + corticosteroids, admission to ICU +/- mechanical ventilation

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Naidoo J et al. J Clin Oncol. 2021;39(35):3978. PMID: 34724386.

Interleukin-6 Inhibitors
Infection Risks

- **Black box warning (tocilizumab, sarilumab)** – bacterial, mycobacterial, fungal, protozoal / OIs
- **Bacterial infections** – severe pneumonia/bronchitis, UTI, cellulitis
- **Viral infections** – herpesviruses, HBV, HCV; HBsAg+ high risk, HBsAg-/HBcAb+ moderate risk
- **Fungal infections** – PJP, cryptococcus, aspergillosis, candidiasis, endemic fungi
- **Mycobacterial infections** – TB, pre-transplant screening
- **Additional considerations**
  - **May mask typical signs and symptoms of infection** (fever, elevated inflammatory markers – CRP)
  - Consider the possibility of disseminated infections
  - **GI perforation risk** – distinct risk with IL-6 inhibitors, particularly in patients with diverticulitis +/- concurrent corticosteroids

Question #2

- 40-year-old male with relapsed B-cell ALL is on day 15 of cycle 3 of **blinatumomab** via continuous infusion through a Hickman catheter. Prophylaxis includes valacyclovir, levofloxacin, fluconazole, and SMX-TMP.
- He develops fevers to 39.0, rigors, tachycardia (HR 120s), and hypotension (82/48), requiring vasopressors, and is transferred to the intensive care unit. He is lethargic but has a non-focal exam, including no tenderness, warmth, or drainage over the Hickman catheter. CXR is non-focal.
- Labs: WBC 1.3 (ANC 400), creatinine of 1.5 (baseline 1.0), normal hepatic panel, and elevated CRP. Blood cultures, urinalysis, and urine cultures are sent.

Which of the following is the most appropriate next step in management?

A. Modify antimicrobials: levofloxacin → IV cefepime + vancomycin and administer tocilizumab
B. Modify antimicrobials: levofloxacin → IV cefepime + vancomycin
C. Modify antimicrobials: fluconazole → IV liposomal amphotericin B
D. Modify antimicrobials: valacyclovir→ IV ganciclovir
E. Administer tocilizumab x 1 dose

Biologic/Targeted Therapies
Bispecific Therapeutics

- T-cell-engaging Bispecific Antibodies (BsAbs; aka BiTE)
- Simultaneously bind to antigens on tumor cells and CD3 subunits on T cells
- Recruit T cells to the tumor → T-cell activation and degranulation→ tumor cell elimination
- Have shown substantial activity in several hematological malignancies targeting
  - CD19 in acute lymphoblastic leukemia → Blinatumomab, first-in-class BiTE
  - CD20 in B-cell non-Hodgkin lymphoma
  - BCMA and GPRC5D in multiple myeloma

Biologic/Targeted Therapies
Blinatumomab – BiTE

- Mechanism/immune defect
  - Bridges CD3+ T cells to CD19+ B cells → forms cytolytic synapse → T-cell activation → release of perforin/granzymes → serial lysis of CD19+ cells (malignant and normal B cells)
  - B-cell aplasia and hypogammaglobulinemia
  - Neutropenia
- Use – B-cell precursor ALL
- Other important considerations
  - Short half-life (2.2 hours), requires continuous infusion x 28 days each cycle→ think about sepsis/CLABSIs**
  - CRS – median onset day 2 and risk greater with earlier than later cycles
  - ICANS
  - Hepatotoxicity, pancreatitis
  - Severe infections – including bacterial (bacteremia, PnA), viral (HSV/VZV, HBV reactivation, CMV PML/JCV rare) and OIs including PJP

Timing in the question stem was KEY – by C3D15, B cells are completely depleted, so there are no CD19+ target cells to trigger T-cell activation. CRS in later cycles quite uncommon →think infection > CRS… mimics are important!

Biologic/Targeted Therapies
Bispecific Therapy in Multiple Myeloma

- **Agents:** 4 currently available; target tumor-associated antigens on myeloma cells
  - BCMA x CD3 – teclistamab, elranatamab, linvoseltamab (IV)
  - GPRC5D x CD3 – talquetamab
- **Mechanism/Immune defect**
  - B-cell, plasma cell aplasia and hypogammaglobulinemia (*particularly with BCMA-targeted therapies)
  - Neutropenia and T-cell exhaustion
  - Immune defects compounded with treatment for CRS/ICANS
- **Infectious risks**
  - Infections #1 cause of non-relapse mortality; BCMA > GPRC5D
  - **Bacterial** – respiratory tract infections, bacteremia
  - **Viral** – respiratory viruses, HSV/VZV, HBV, CMV, JCV-PML (rare)
  - **Fungal** – PJP and opportunistic molds and endemics
- **Prevention**
  - **Viral ppx** – e.g., (val)acyclovir, indefinitely on therapy
  - **PJP ppx** – duration of therapy + ≥ 6 months and CD4 ≥ 200 (whichever longest)
  - **Bacterial/fungal ppx** – for ANC < 500
  - Supplemental IVIG, update vaccinations PRIOR to start

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Neutropenic Fever and "Syndromes"

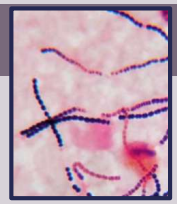
Question #3

- 70-year-old male with AML and recent initiation of azacitidine and venetoclax presenting with neutropenic fever (102F) and fatigue
- VS – 120/80, HR 100, RR 14, Sa02 96% on ambient air
- Exam – no significant OP lesions, lungs CTA, abd soft, nt/nd, no peri-rectal lesions/pain, no skin rash or lesions, no pain/redness/tenderness over central access site
- Cultures – blood/urine pending
- CXR – non-focal
- Current prophylaxis – levofloxacin and acyclovir
- Prior infection history – none

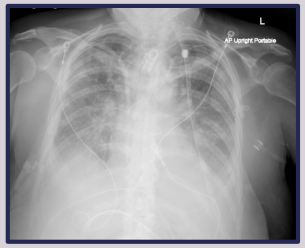
Which of the following is the most appropriate change in therapy?

A. Levofloxacin → IV cefepime
B. Levofloxacin → IV cefepime + vancomycin
C. Levofloxacin → IV cefepime + metronidazole
D. Acyclovir → IV ganciclovir
E. Addition of antifungal therapy

Question #4



- 35-year-old woman with AML, day 15 of induction therapy. Presentation - fever, chills, diffuse erythematous rash
- Exam – 100/62, HR 120, grade 2 oral mucositis, diffuse, blanching, erythematous rash
- Cultures - blood cultures with GPC in chains.
- CXR - bilateral diffuse infiltrates
- Prophylaxis - levofloxacin and acyclovir



Which organism is the most likely cause of this infection?

A. Streptococcus pneumoniae
B. Coagulase-negative Staphylococcus
C. Enterococcus faecalis
D. Streptococcus mitis
E. Stomatococcus mucilaginosus

Viridans Group Streptococci (VGS)

- VGS include S. mitis, S. oralis, S. sanguinis
- Portal of entry: normal flora of the oral cavity, upper respiratory, and GI/GU tract
- Clinical presentation
  - Can include fevers, chills, flushing, stomatitis, pharyngitis
  - VGSS - **toxic shock-like syndrome**
    - Early vs late (2–3 days after presentation)
    - Hypotension→ respiratory failure→ **ARDS**
    - Maculopapular rash – centrifugal spread +/- palmar/sole desquamation
- Risk factors: profound neutropenia (AML, HCT), oral mucositis, high-dose cytarabine, fluoroquinolone prophylaxis, prior VGS
- Treatment: beta-lactams (increasing PCN resistance), **vancomycin (VGSS/ARDS)**

Shelburne et al. Clin Infect Dis. 2014;59(2):223.
Toonkel AR, Sepkowitz KA. Clin Infect Dis 2002;34(11):1524.

Board Testable Scenarios: Breakthrough BSIs

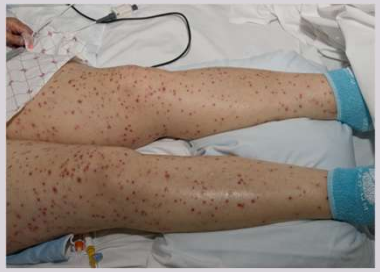
- Typical patient - neutropenic, progressive sepsis
- Recognize clinical presentation and holes in antimicrobial coverage
  - **ARDS, rash, quinolones, mucositis** → viridans Streptococci
  - **Sepsis with β-lactams** → Extended-spectrum (ESBL) and AmpC β-lactamase-Producing Enterobacterales +/- Stenotrophomonas
  - **Sepsis with carbapenems** → Carbapenem-resistant Enterobacterales/Acinetobacter baumannii, Stenotrophomonas (and other beta-lactams)
  - **Sepsis with broad-spectrum antibiotics** → Vancomycin-resistant Enterococcus (VRE)
  - **Lung and skin lesions** → P. aeruginosa (Ecthyma gangrenosum), fungi, Nocardia
  - **Mucositis (upper, lower tract)** → Fusobacterium spp., Clostridium spp including C. septicum, Rothia mucilaginosa

Question #5

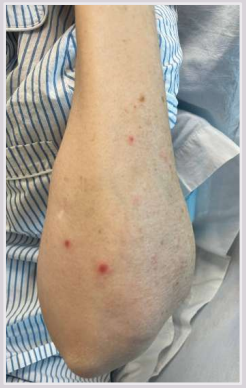
- 59-year-old woman with AML with neutropenia for 25 days and febrile for 6 days. She is receiving meropenem, vancomycin and acyclovir. Now with new skin lesions that are small, tender papules without central ulceration.

This is most consistent with infection with which of the following organisms?

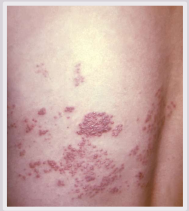
A. Rhizopus spp.
B. Varicella zoster virus
C. Cryptococcus neoformans
D. Vancomycin resistant Enterococci
E. Candida tropicalis

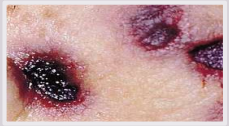


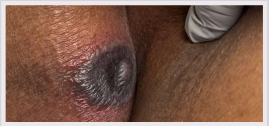
Skin Lesions



- Candidiasis
  - Small, tender papules
- Herpes
  - Vesicular
- Aspergillus
  - Ulcerative, necrotic
- P. aeruginosa
  - Ecthyma gangrenosum
- Other filamentous fungi (Fusarium spp, Scedosporium spp)

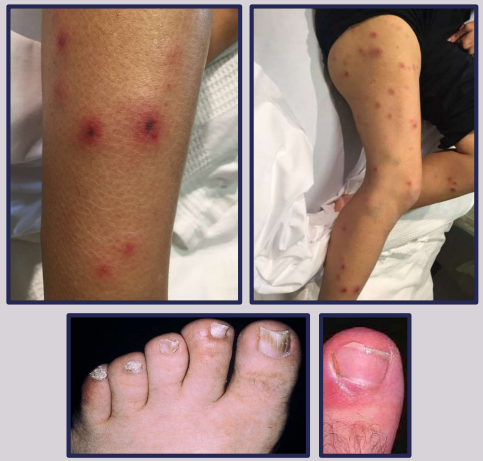






- 35-year-old woman with relapsed AML with dense neutropenia for over 30 days
- Ongoing fevers with rapidly progressing, painful papular and nodular lesions, varying stages, some with central necrosis.
- Receiving meropenem, vancomycin, micafungin and acyclovir.
- Micro lab update that blood cultures are growing a “mold”

FUSARIOSIS

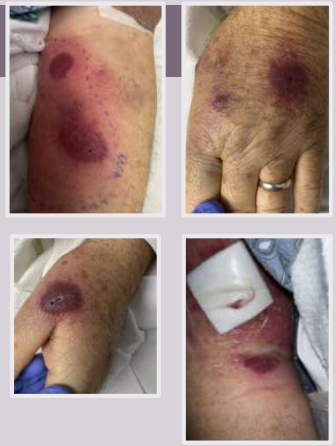


Question #6

- 70-year-old male with newly diagnosed AML developed erythematous, tender and edematous plaques over sites of trauma (blood draws, peripheral IV). He has been febrile to 38.7°C for the past several days.

What is the most likely etiology?

A. Candida albicans
B. Sweet’s syndrome
C. Aspergillus niger
D. Varicella Zoster virus
E. Pseudomonas aeruginosa



Sweet’s Syndrome

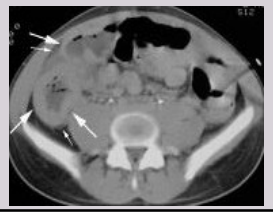
- Acute febrile neutrophilic dermatosis
- **Variants**
  - Classic (idiopathic)
  - Malignancy-associated (hematologic, most common – **AML**, MDS), often precedes or coincides with diagnosis
  - Drug-induced (e.g., G-CSF as trigger, bortezomib, others)
- **Clinical Presentation**
  - Skin (most common) - tender erythematous plaques and nodules (typical); also bullous, cellulitic, subcutaneous, and necrotizing lesions
  - Can demonstrate **pathergy** (lesions at site of trauma/injury)
  - Extracutaneous – can involve virtually any organ system (e.g., eyes, lungs, joints, kidney, CNS)
- **Classic Stem** – neutropenia→ **G-CSF initiated**→ neutropenia resolving→ fever + tender skin lesions→ cultures negative and biopsy shows dense dermal neutrophilic infiltrate
- **Treatment** – steroids (first-line); in cases of malignancy, treatment targeted at underlying disease

Question #7

- 70-year-old woman with AML receiving induction chemotherapy and neutropenic for 15 days. Develops fever, diarrhea and abdominal pain. Exam with decreased bowel sounds and tenderness with deep palpation in her RLQ. CT shows inflammation in cecum. Receiving levofloxacin and fluconazole prophylaxis. Four days prior to her admission for chemotherapy she ate out at a Chinese restaurant and had fried rice.

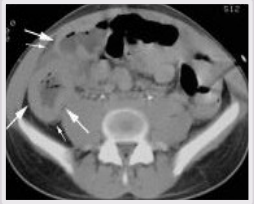
Which is the most likely etiology?

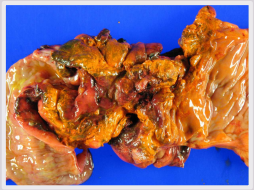
A. Norovirus
B. Clostridioides (Clostridium) difficile
C. Mixed anaerobic and aerobic bacteria
D. Candida albicans
E. Bacillus cereus



Neutropenic Enterocolitis

- AKA typhlitis, ileocecal syndrome (Greek: typhlon = cecum)
- **Mechanism:** chemotherapy-induced mucosal injury → secondary bacterial/fungal invasion of bowel wall during neutropenia → transmural necrosis
- **Risks**
  - Cytotoxic chemotherapy (e.g., high-dose cytarabine) +/- steroids
  - Dense neutropenia
- **Clinical Presentation**
  - Fever + abdominal pain + neutropenia
  - Can be accompanied by bacteremia (hint: mixed, anaerobic with C. septicum, C. tertium, Bacteroides spp)
- **Microbiology:** polymicrobial with gram-negative, gram-positive, anaerobic bacteria and fungi
- **Diagnostics:** CT imaging (mural thickening, fat stranding, pneumatosis)
- **Management:** medical (supportive care, IV antimicrobials +/- G-CSF), less often surgical management
- **Relevant DdX:** C difficile, viral colitis (CMV, adenovirus), GVHD, acute appendicitis





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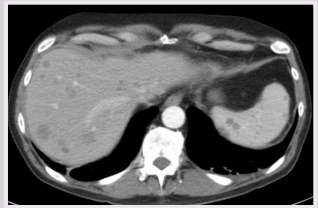
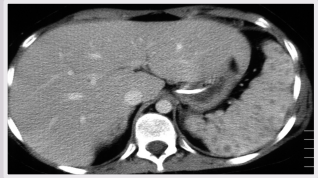
From: Xia R, Zhang X. World J Gastrointest Pathophysiol 2019;10(3):36.

Hepatosplenic Candidiasis

- Form of chronic disseminated candidiasis, primarily involves liver & spleen, occasionally other organs – kidney
- **Clinical Clues**
  - Hematologic malignancy, prolonged neutropenia, not improving on broad-spectrum antibiotics
  - Fever, abdominal/flank pain, hepatosplenomegaly, nausea/vomiting
  - Neutrophil recovery/engraftment (typically occurs within 2 weeks)
  - Labs: abnormal hepatic panel (↑alk phos)
- **Microbiology** – C. albicans most common, C. tropicalis, alt Candida spp
- **Diagnostics**
  - **Blood cultures often negative**, role of BDG, biopsy
  - Imaging: more sensitive AFTER neutrophil recovery – US, CT, MRI
- **Differential** – other fungi, bacteria/mycobacteria, underlying cancer
- **Treatment** – echinocandin or lipid formulation of amphotericin B, step-down course with oral azole (+/- steroids)





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Pappas PG. Clin Infect Dis. 2016;62(4):e1.

Infections in Neutropenic Cancer Patients Summary of Key Points

- Recognize typical infections associated with neutropenia and/or immunomodulatory therapies
- Predict breakthrough pathogens based on applied therapies
- Know specific syndromes
  - VGS sepsis
  - Differential of skin lesions
  - Invasive fungal infections in neutropenic patients
    - Sinopulmonary
    - Bloodstream
    - Hepatosplenic candidiasis
  - Neutropenic enterocolitis

Thank You

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