WEST Coast TxID Conference

June 11th 2025

Paulina Vega MD

ID Fellow UW/FHCC

[redacted] y.o [redacted] with ALL Ph+ s/p recent Blinatumomab awaiting haploidentical (mother) PBSCT.

- Presents with generalized weakness, dizziness and shortness of breath on standing and bright red blood in stool.
- Admitted to ICU for pancytopenia and hypotension with tachycardia.
- Prolonged neutropenia ~3 months.

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- Prophylaxis meds
  - Bactrim MWF
  - Fluconazole 400mg daily
  - Acylcovir 400 mg BID
  - Cefdinir 300 mg BID (allergy to levofloxacin)

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- Pan-scanned:
  - CT Chest: multifocal bilateral consolidations and groundglass opacities with subtle cavitary component in the RUL.

- ID is consulted.

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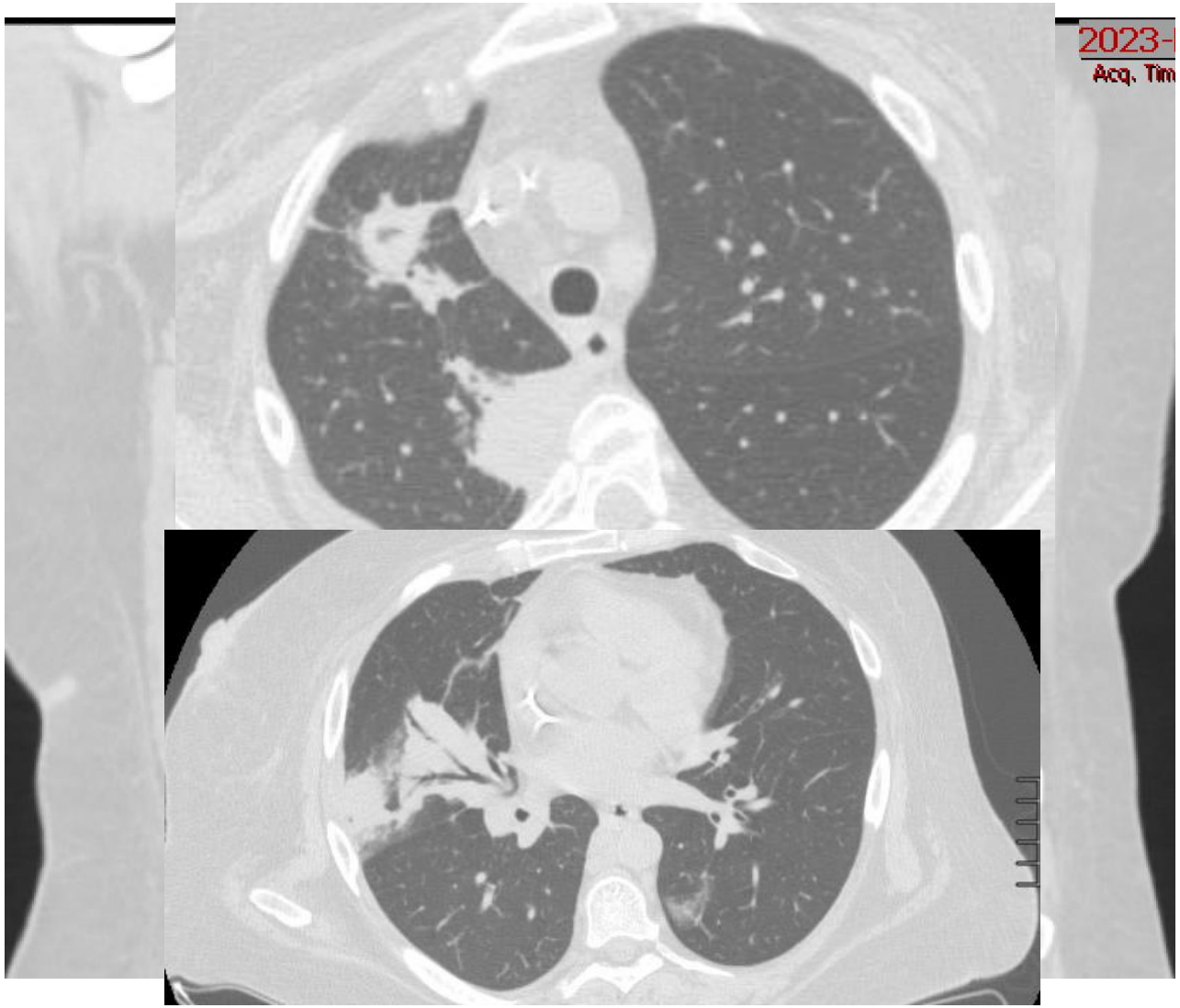
Prolonged neutropenia ~3 months.
New pulmonary consolidations and GGOs

- Poll question: What's at the top of your differential diagnoses?

  - Invasive mold infection. - it's always mold.
  - Endemic fungi – are you hiding social history for a reason?
  - Bacterial – you're missing a lot of gram negative coverage with cefdinir
  - Viral – CMV, respiratory viruses: fall season
  - Non-infectious

Pulmonary consolidations in neutropenic patient DDX?

- Invasive fungal disease:
  - Aspergillus
  - Mucorales
  - Fusarium
  - Cryptococcus
  - Endemic fungi
- Viruses
  - CMV
  - Adenovirus
  - RSV
  - Other respiratory viruses
- Bacterial
  - PJP
  - Legionella
  - Mycoplasma
  - Gram+ Gram –
  - Nocardia
  - Toxoplasmosis
  - Mycobacteria



- Non infectious
  - Lymphoma
  - Posttransplant lymphoproliferative disease
  - Pulmonary hemorrhage
  - COP
  - Leukemic infiltrates
  - Peri-engraftment respiratory distress syndrome.

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New pulmonary consolidations and GGOs

- <u>ID's social history</u>
- Travel hx:
  - Lived in Arizona
  - Been to Ohio
- Jobs
  - [redacted] lumber department for the last 2 years.
  - Cleaning company x 2 years.
  - Call center x 10 years
- No tobacco, EtOH or IVDU. Occasional marijuana gummy.
- 7 tattoos >5 years old, performed in a tattoo parlor
- Pets: 1 cat

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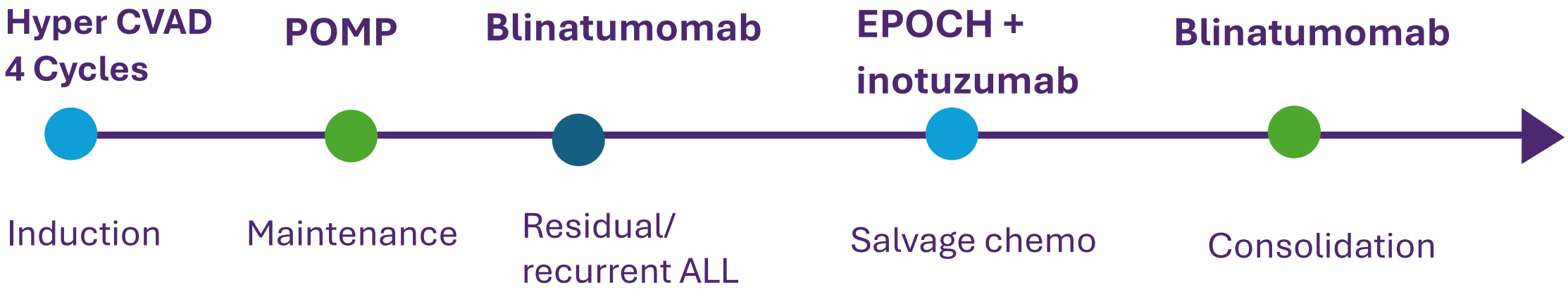
- Oncology hx timeline



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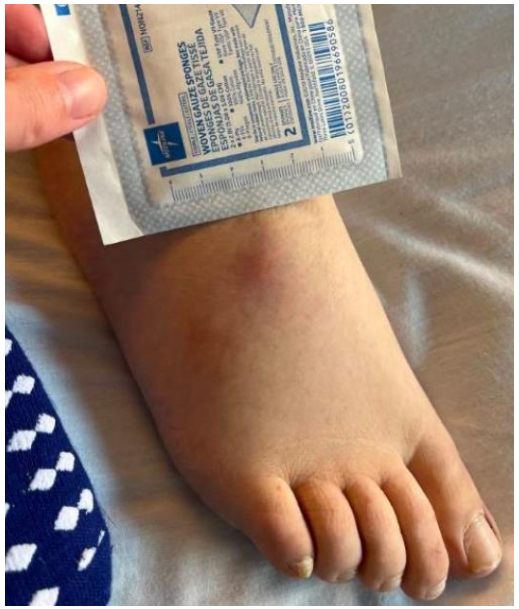
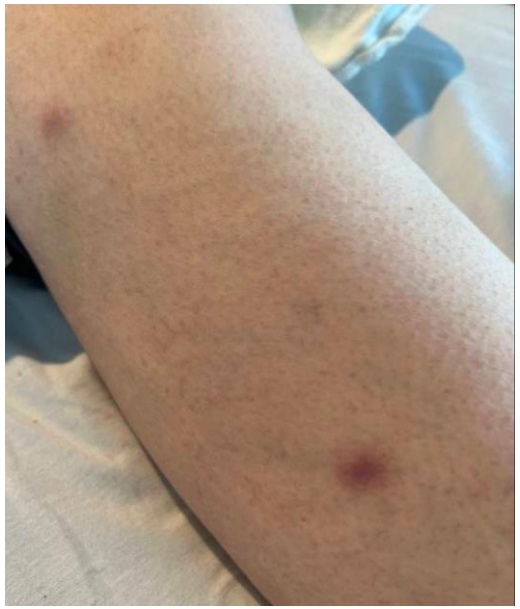
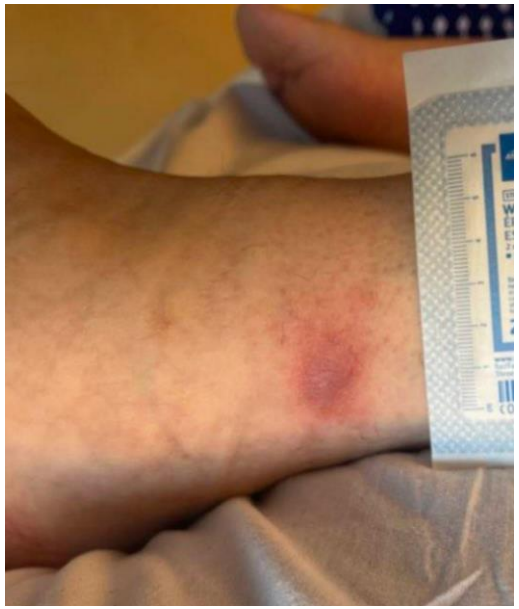
New pulmonary consolidations and GGOs

- ID's physical exam


BP: 83/64, HR: 104, SpO2: 98% RA, RR: 20, T: 37.2
WBC 0.5, ANC 0.3, ALC 0.18. Hgb 3.5. PLT 15. INR 1.6.

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Prolonged neutropenia ~3 months.
New pulmonary consolidations and GGOs and new skin nodules.

- Poll question: Empiric treatment initiation

A. AmBisome® and micafungin
B. AmBisome® and Posaconazole
C. AmBisome® and voriconazole
D. AmBisome® monotherapy
E. Posaconazole monotherapy
F. Voriconazole monotherapy

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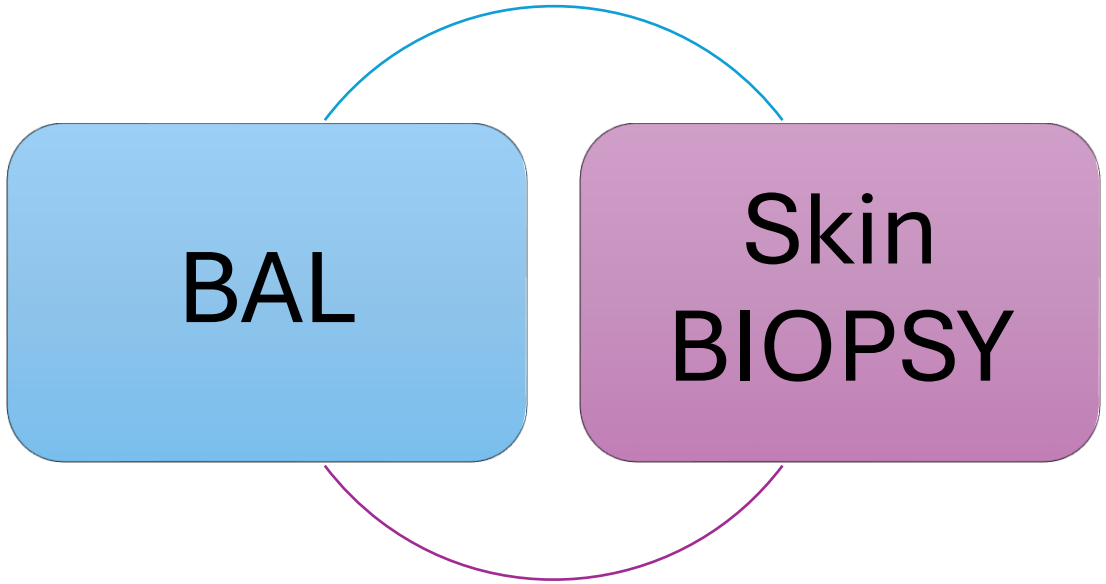
- Next steps



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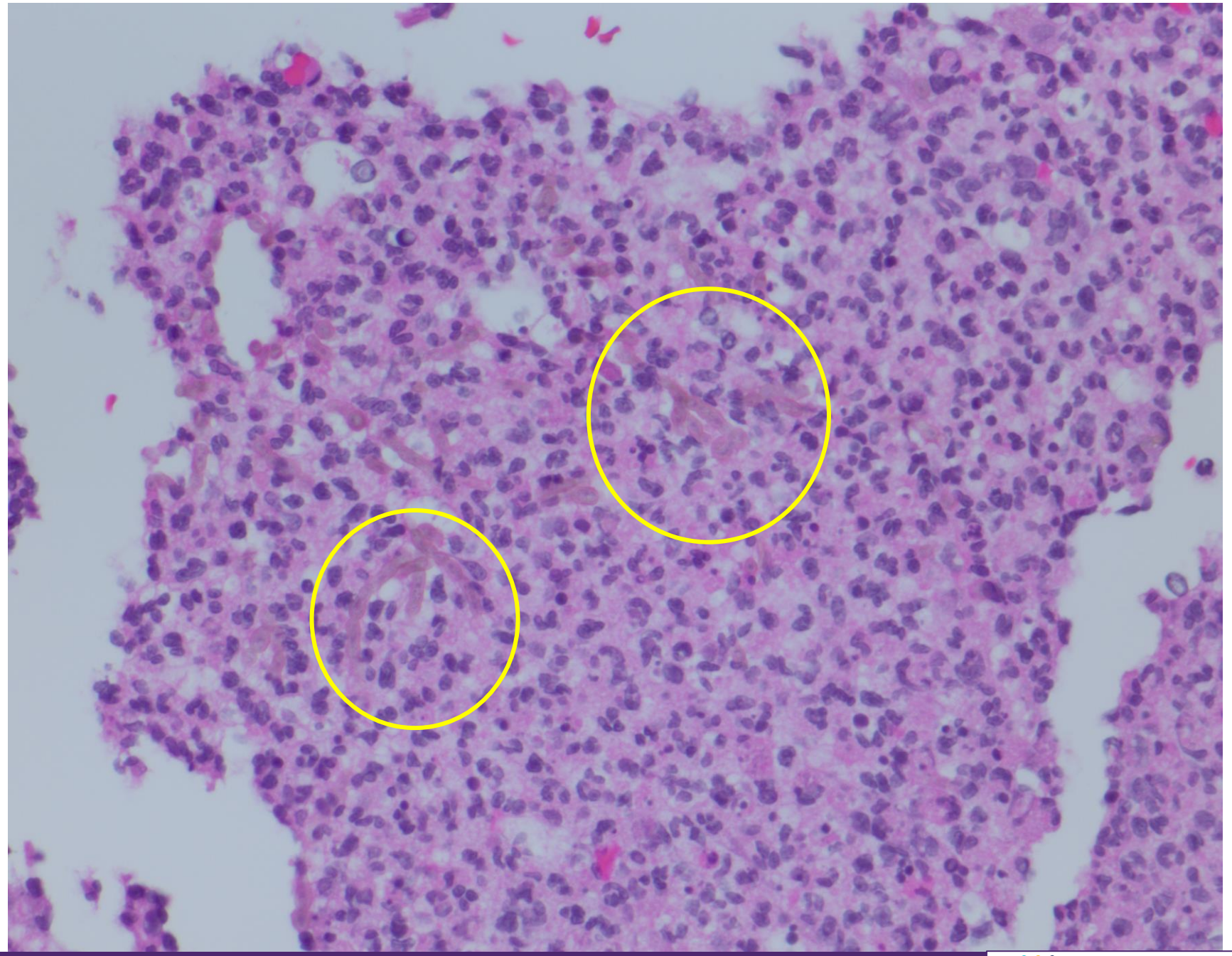
BAL results

- RML
  - Mucorales PCR negative
  - Legionella PCR negative
  - Fungal PCR negative
  - Aspergillus PCR negative
  - Nocardia cx negative
  - Culture gram stain negative, OP flora
  - Fungal culture: *candida glabrata*
- AFB negative
- RUL
  - Fungal PCR: *Aspergillus Fumigatus*
  - Aspergillus PCR: *Aspergillus Fumigatus*
  - Aspergillus GM: >7.3
  - Fungal culture: *candida glabrata*

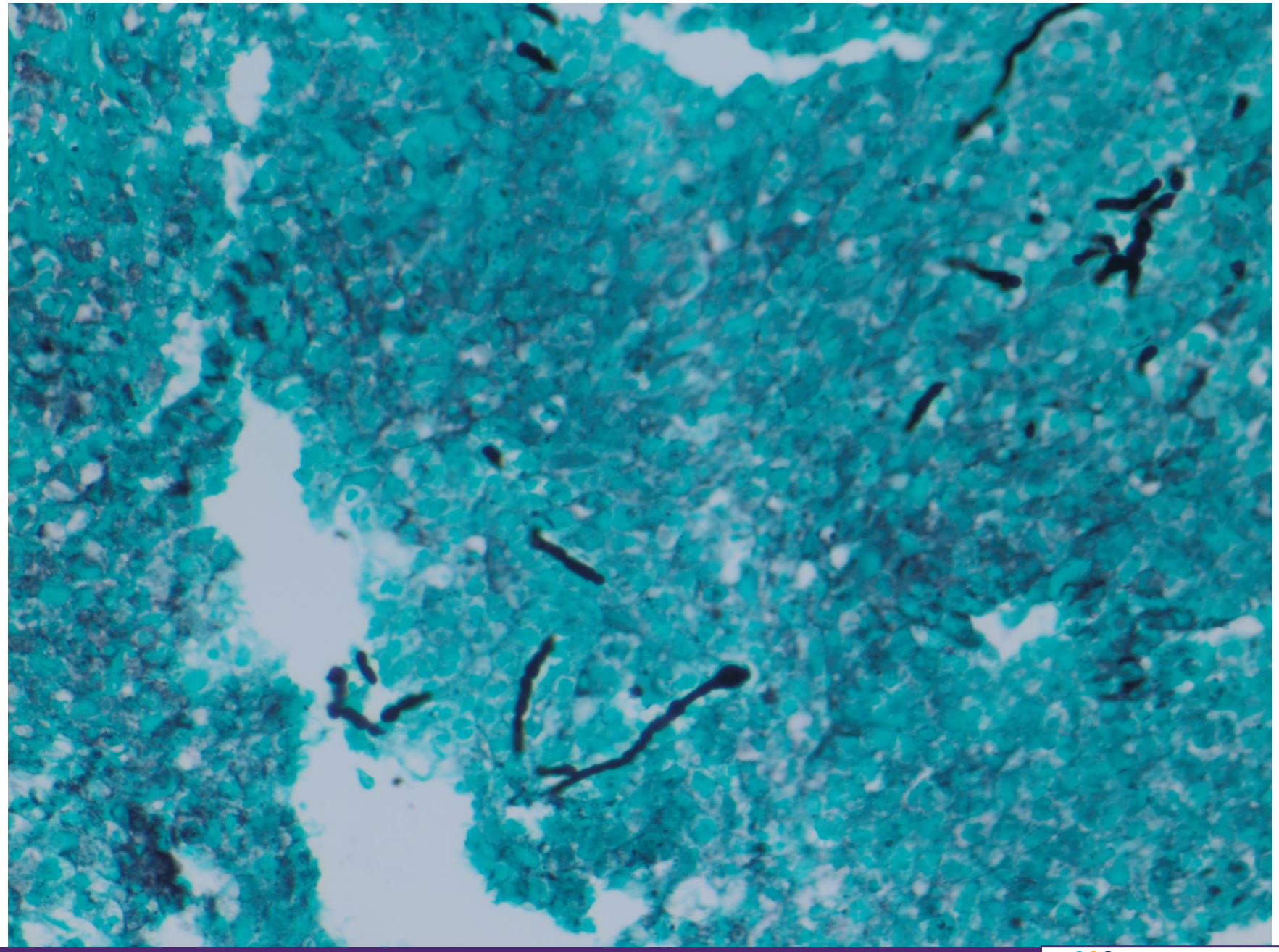
Skin biopsy

- What kind of stain is this?
- What do you see?

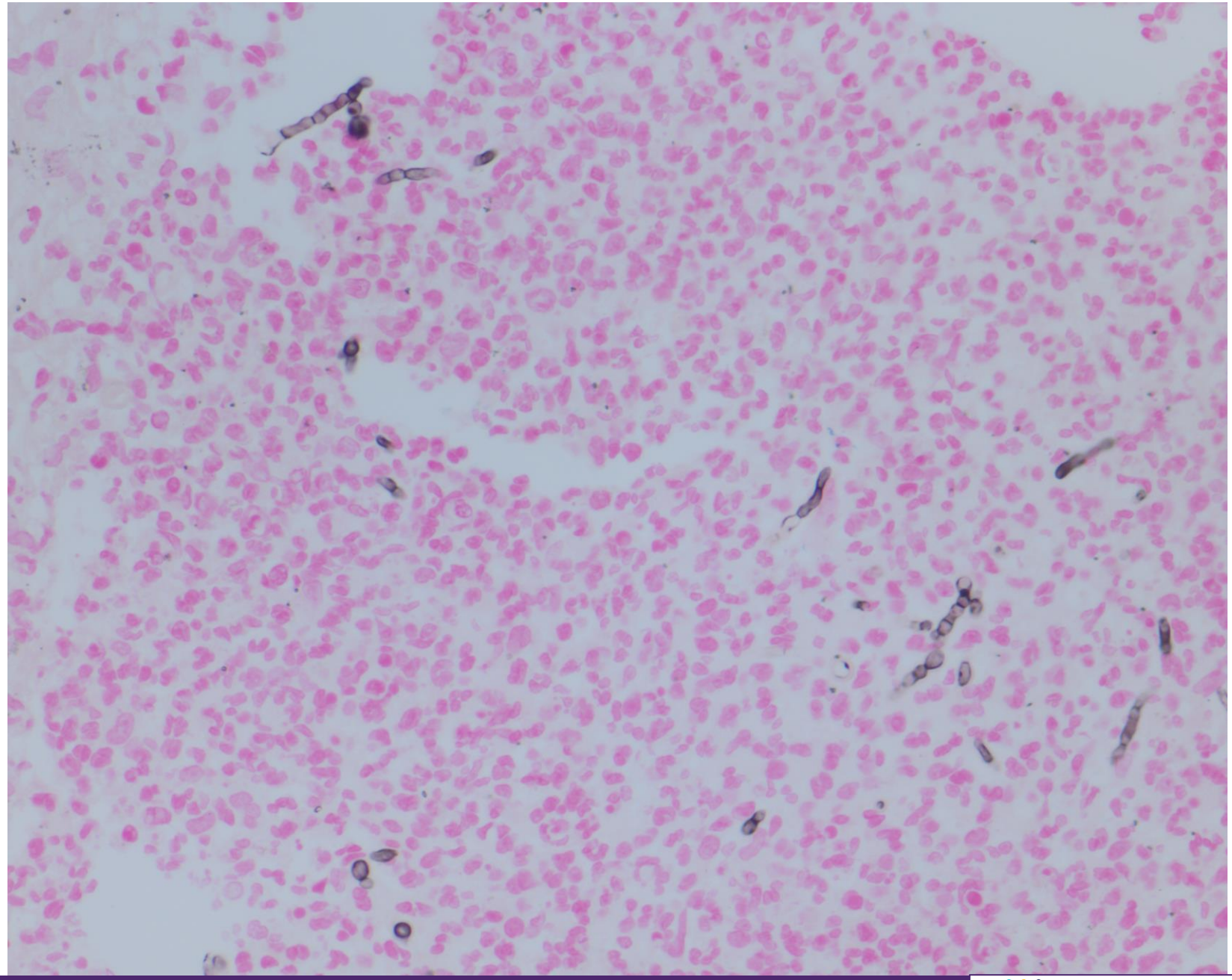
- Hematoxylin and eosin (H&E) stain and may show pigmented hyphae



Gomori’s methenamine silver stain



Fontana–Masson stain



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Prolonged neutropenia ~3 months.
New pulmonary consolidations and GGOs and new skin nodules.
BAL + GM and *Aspergillus Fumigatus*.

- Poll question: Any guesses?

A. Aspergillus non fumigatus spp
B. Fusarium species complex
C. Mucorales
D. phaeohyphomycosis.
E. Dematiaceous fungi
F. Candida albicans

Path report of skin tissue

The presence of melanin within the fungal wall is consistent with **phaeohyphomycosis**.

Slides	Test	Result
A1-2	Gomori's Methenamine Silver	Highlights fungal hyphae with septations.
A1-3	Fontana Masson	Highlights melanin within fungal walls of hypha

- Invasive filamentous fungi with likely melanin pigment is seen in the subcutaneous tissue. Histology is not able to speciate, but the morphology is concerning for phaeohyphomycosis.

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Skin biopsy results

- Fungal PCR: *Exophiala dermatitidis* or *Exophiala dopicola*
- Mucorales PCR negative
- Aspergillus PCR negative
- Fungal culture: *Exophiala dermatitidis*

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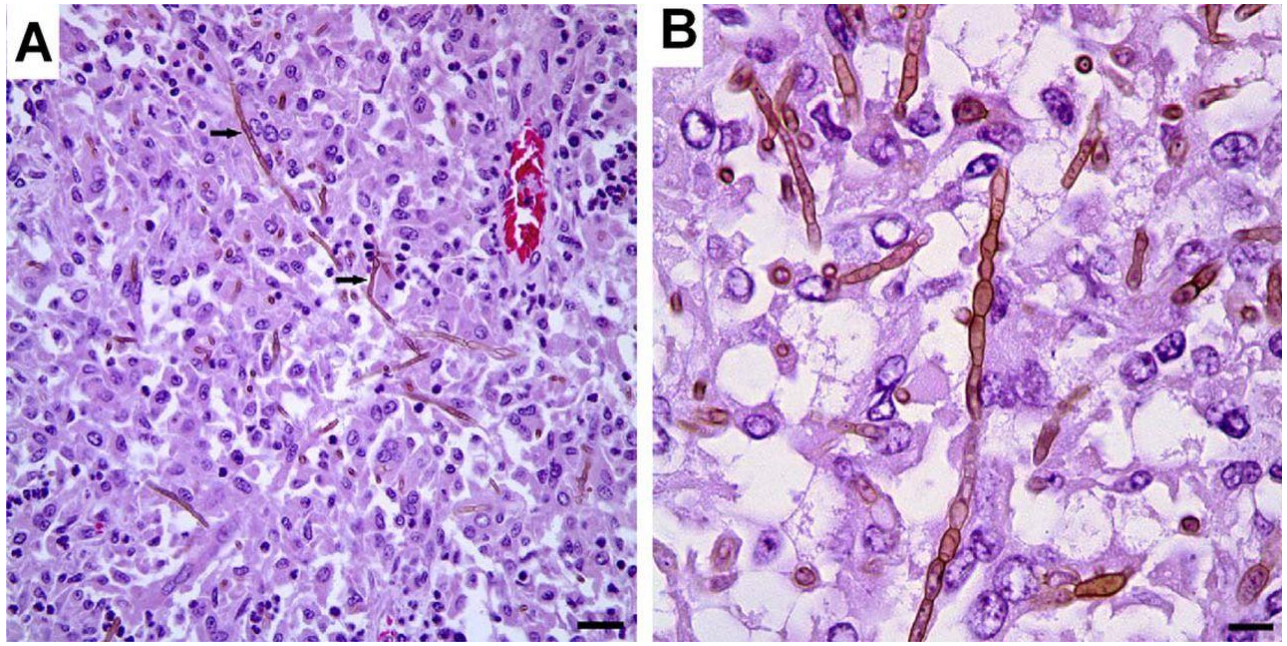
BAL + GM and *Aspergillus Fumigatus*. Tissue (skin) + *Exophiala dermatitidis*

- Poll question: Now, how would you treat?

A. Continue Ambisome and voriconazole
B. Voriconazole monotherapy
C. Ambisome + Vori + Terbinafine
D. Vori + Micafungin
E. Posaconazole monotherapy
F. Vori + Terbinafine

Phaeohyphomycosis

- Phaeohyphomycosis is a cluster of infectious syndromes caused by a group of darkly pigmented fungi, often referred to as “dematiaceous” or “melanized” molds in the literature.



>150 species and 70 genera implicated in human disease.
The term phaeohyphomycosis was coined in 1974 referring to tissue invasion by pigmented septate hyphae and describes a large variety of clinical syndromes.

Clinical syndromes a/w Phaeohyphomycosis

Clinical syndrome	Associated melanized fungi	Suggested therapy
Allergic fungal sinusitis	*Curvularia*	Surgery + steroids ± Vori
Allergic bronchopulmonary mycosis	*Curvularia*	Steroids ± Vori
Subcutaneous nodules	*Alternaria*, *Exophiala*, *Phialophora*	Surgery ± Vori
Invasive sinusitis	*Curvularia*, *Alternaria*, *Exserohilum*	Surgery + L-AmB ×2 wk followed by Vori
Bone and joint infections	*Lomentospora*, *Alternaria*, *Exophiala*, *Phialophora*	Surgery + Vori or Posa
Catheter-related peritonitis	*Curvularia*, *Exophiala*, *Alternaria*	Catheter removal + systemic antifungal therapy
Pneumonia	*Verruconis*, *Exophiala*, *Chaetomium*, *Alternaria*	L-AmB if severe otherwise Vori or Posa, surgery for nodules in immunocompetent patients
CNS disease	*Cladophialophora*, *Curvularia*, *Rhinocladiella*, *Verruconis*, *Exophiala*, *Fonsecaea*	Complete excision + combination therapy (see text)
Disseminated disease	*Lomentospora*, *Exophiala*, *Curvularia*, *Alternaria*	See text for discussion

Arcobello, J. T., & Revankar, S. G. (2020).

Dematiaceous fungi associated with invasive disease

Arcobello, J. T., & Revankar, S. G. (2020).

Genera	Associated manifestations	Special comment
Alternaria	Allergic, sinusitis, disseminated, CNS, osteoarticular, pulmonary, CAPD	Mainly immunosuppressed
Acrophialophora	Pulmonary, CNS	Very rare
Aureobasidium	Disseminated, CNS, Osteoarticular, CAPD	Mainly immunosuppressed, common laboratory contaminant
Chaetomium	CNS, pulmonary, sinusitis	IVDA is a risk factor; sinusitis may occur in immunocompetent
Cladophialophora	CNS, disseminated, osteoarticular, pulmonary	Neurotropic in immunocompetent
Curvularia	Allergic, sinusitis, disseminated, CNS, CAPD, pulmonary	May affect immunocompetent
Exserohilum	Allergic, sinusitis	Mainly immunocompromised
Exophiala	Disseminated, osteoarticular, CNS, pulmonary, CAPD	Neurotropic if disseminated
Fonsecaea	Disseminated, osteoarticular, CNS	Agent of chromoblastomycosis but rarely invades
Lomentospora	Disseminated, pulmonary, osteoarticular, CNS	Mainly immunosuppressed
Microascus	CNS, pulmonary, disseminated	Mainly immunosuppressed
Phaeoacremonium	Disseminated	Mainly immunosuppressed
Phialemonium	Disseminated, CAPD	Very rare
Phialophora	Osteoarticular	Very rare
Rhinocladiella	CNS	Neurotropic in immunocompetent
Verruconis	CNS, disseminated, pulmonary	Neurotropic; almost all cases are immunosuppressed

Phaeohyphomycosis

- Ubiquitous, present in soil.
- Specific niches: Exophiala species - toxic mines and steam baths.

- Subq lesions – minor trauma is the usual inciting factor

Arcobello, Revankar. Semin Respir Crit Care Med(2020)
Wong, Revankar. Inf Dis Clin N Am (2016)

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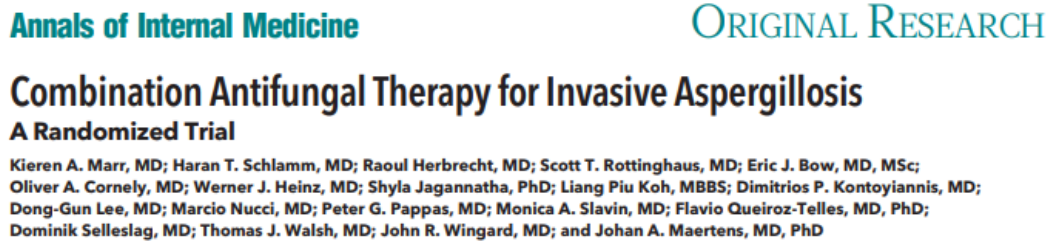
- Poll question: I'm curious. Do you use dual therapy for Invasive pulmonary aspergillosis?

A. Yes, always.

B. Yes, selected cases.

C. Never.


Annals of Internal Medicine ORIGINAL RESEARCH

Combination Antifungal Therapy for Invasive Aspergillosis

A Randomized Trial

Kieren A. Marr, MD; Haran T. Schlamm, MD; Raoul Herbrecht, MD; Scott T. Rottinghaus, MD; Eric J. Bow, MD, MSc; Oliver A. Cornely, MD; Werner J. Heinz, MD; Shyla Jagannatha, PhD; Liang Piu Koh, MBBS; Dimitrios P. Kontoyiannis, MD; Dong-Gun Lee, MD; Marcio Nucci, MD; Peter G. Pappas, MD; Monica A. Slavin, MD; Flavio Queiroz-Telles, MD, PhD; Dominik Selleslag, MD; Thomas J. Walsh, MD; John R. Wingard, MD; and Johan A. Maertens, MD, PhD

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Hospital course:

- She had EGD/Colonoscopy done.
- Found to have several ulcerated nodules in colon.
- We were concerned of fungal invasion in colon.
- But biopsy x2 were negative for fungal disease.
- Her planned haplo donor was medically deferred.

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Clinical outcome:

- 1 month outpatient f/u:
  - Chest CT revealed multiple B/L nodule slightly decreased in size
- Voriconazole level: therapeutic.
- Asymptomatic.
- 2 months post: CAR-T cell therapy with bridging w/ Inotuzumab.
- C/b CRS, polymicrobial bacteremia, fungemia, GI bleed, recurrent c diff.
- Autopsy report: Relapsed/refractory B-Cell acute lymphocytic leukemia and Recurrent *Clostridium difficile* colitis infection with pseudomembranes and superimposed invasive *Candida glabrata* infection in small and large bowel

Literature review: Mixed fungal infections

Mixed fungal infections- Epidemiology

Epidemiology and outcomes of patients with invasive mould infections: a retrospective observational study from a single centre (2005–2009)

Lena Klingspor,[1] Baharak Saaedi,[1] Per Ljungman[2] and Attila Szakos[3]

[1]Division of Clinical Microbiology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden, [2]Division of Haematology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden and [3]Division of Pathology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

- Single center study from Stockholm
- Epi and outcome on IMI from 2005-2009
- N = 100
- (13) = >1 mold was identified → 7 proven / 6 probable
  - IA + Invasive mucormycoses (6)
  - IA + Fusariosis (2)
  - IA + *S. apiospermum* + *Scyalicidium dimediatum* (1)
  - IA + *Fusairum solani* + *Saksenia vasiformis* + *S. apiospermum* + *S. dimediatum* (1)
  - Two aspergillus spp
- (3) had Hematologic malignancies. (AML and ALL)
- (4) Allo HSCT
- (1) Solid tumor
- Infections
  - (2) had disseminated
  - (5) pulmonary
  - (2) pulm + sinusitis
  - (2) deep wound infections

Klingspor. Mycoses. (2015)

Mixed fungal infections– Epidemiology

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Medical Mycology, 2021, 59, 50–57
doi:10.1093/mmy/myaa029
Advance Access Publication Date: 13 May 2020
Original Article

Original Article

Epidemiology of visceral mycoses in patients with acute leukemia and myelodysplastic syndrome: Analyzing the national autopsy database in Japan

Tomiteru Togano[1,2,*], Yuhko Suzuki[3], Fumihiko Nakamura[1], William Tse[2] and Hikaru kume[4]

- Retrospective review (1989-2015).
- N = 7183 autopsy reports with Acute leukemia and MDS
- N =1562 visceral mycoses
- Mixed infection = 6.5% (total)

Togano. Med mycology. 2021

Mixed mold infections– Epidemiology

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Tomiteru Togano[1,2,*], Yuhko Suzuki[3], Fumihiko Nakamura[1], William Tse[2] and Hikaru kume[4]

Table 2. Comparison of combination of causative agents in cases with complicated infection in acute leukemia and MDS.

Year	1989		1993		1997		2001		2005		2009		2013		2015		Total	
Causative agents	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Aspergillus + *Candida*	23	(71.9)	13	(68.4)	7	(77.8)	8	(66.7)	3	(33.3)	4	(50.0)	1	(33.3)	2	(20.0)	61	(59.8)
Aspergillus + *Mucormycetes*	3	(9.4)	2	(10.5)	0	(0.0)	2	(16.7)	2	(22.2)	1	(12.5)	0	(0.0)	2	(20.0)	12	(11.8)
Aspergillus + *Cryptococcus*	0	(0.0)	0	(0.0)	1	(11.1)	1	(8.3)	1	(11.1)	1	(12.5)	1	(33.3)	1	(10.0)	6	(5.9)
Aspergillus + *Trichosporon*	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)
Aspergillus + Unknown*	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(20.0)	2	(2.0)
Candida + *Cryptococcus*	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)
Candida + *Mucormycetes*	6	(18.8)	2	(10.5)	1	(11.1)	0	(0.0)	1	(11.1)	1	(12.5)	0	(0.0)	0	(0.0)	11	(10.8)
Candida + Unknown*	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)
Mucormycetes + Unknown*	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	2	(20.0)	3	(2.9)
Aspergillus + *Candida* + *Cryptococcus*	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Aspergillus + *Mucormycetes* + *Cryptococcus*	0	(0.0)	1	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.0)
Other	0	(0.0)	0	(0.0)	0	(0.0)	1	(8.3)	0	(0.0)	0	(0.0)	1	(33.3)	1	(10.0)	3	(2.9)
Total	32	(100)	19	(100)	9	(100)	12	(100)	9	(100)	8	(100)	3	(100)	10	(100)	102	(100)

*Unknown: an unidentified fungus in the infected organ.

Togano. Med mycology. 2021

Mixed fungal infections– Epidemiology

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Epidemiology of visceral mycoses in patients with acute leukemia and myelodysplastic syndrome: Analyzing the national autopsy database in Japan

Tomiteru Togano[1,2,*], Yuhko Suzuki[3], Fumihiko Nakamura[1], William Tse[2] and Hikaru kume[4]

Table 3. Annual proportion of severe infections by causative agents in acute leukemia and MDS.

Year	1989	1993	1997	2001	2005	2009	2013	2015	Total
Number of severe / total cases (%)									
Monopathogens									
Aspergillus	69/117	87/124	53/113	88/131	59/91	30/52	15/40	26/35	427/703
	(59.0)	(70.2)	(46.9)	(67.2)	(64.8)	(57.7)	(37.5)	(74.3)	(60.7)
Candida	82/128	39/61	30/51	18/43	15/25	15/22	4/9	10/15	213/354
	(64.1)	(63.9)	(58.8)	(41.9)	(60.0)	(68.2)	(44.4)	(66.7)	(60.2)
Cryptococcus	5/10	2/2	0/3	5/5	1/2	1/1	0/2	1/2	15/27
	(50.0)	(100)	(0.0)	(100)	(50.0)	(100)	(0.0)	(50.0)	(55.6)
Mucormycetes	11/21	14/22	9/16	18/22	17/19	5/5	14/15	11/12	99/132
	(52.4)	(63.6)	(56.3)	(81.8)	(89.5)	(100)	(93.3)	(91.7)	(75.0)
Trichosporon	1/2	1/1	1/1	0/0	1/2	0/0	0/0	0/0	4/6
	(50.0)	(100)	(100)	(0.0)	(50.0)	(0.0)	(0.0)	(0.0)	(66.7)
Others	0/0	0/0	0/0	0/0	1/1	0/1	2/2	1/1	4/5
	(0.0)	(0.0)	(0.0)	(0.0)	(100)	(0.0)	(100)	(100)	(80.0)
Unknown*	42/64	27/46	16/29	17/30	11/23	5/10	9/15	11/16	138/233
	(65.6)	(58.7)	(55.2)	(56.7)	(47.8)	(50.0)	(60.0)	(68.8)	(59.2)
Complicated**	19/32	13/19	7/9	10/12	5/9	6/8	2/3	10/10	72/102
	(59.4)	(68.4)	(77.8)	(83.3)	(55.6)	(75.0)	(66.7)	(100)	(70.6)
Total	229/374	183/275	116/222	156/243	110/172	62/99	46/86	70/91	972/1562
	(61.2)	(66.5)	(52.3)	(64.2)	(64.0)	(62.6)	(53.5)	(76.9)	(62.2)

Togano. Med mycology. 2021

Mixed fungal infections– Epidemiology

Fungal infection in post-renal transplant patient: Single-center experience

Krishan L. Gupta, Sahil Bagai, Raja Ramachandran, Vivek Kumar, Manish Rathi, Harbir S. Kohli, Ashish Sharma[1], Arunaloke Chakrabarti[2]

Departments of Nephrology, [1]Renal Transplant Surgery and [2]Microbiology, PGIMER, Chandigarh, India

- Single center retrospective review (2014-2017)
- Fungal infections in post-renal tx recipients
- N = 550 (total renal transplants)
  - 56 - IFI
  - 20 – Dual infection (but includes bacteria and viral co-infection)
    - Aspergillus + (mucormycosis, bacteria [unspecified], scedosporium, mycobacteria)
    - PJP + (CMV, Nocardia)

Gupta et al. Indian Journal of Pathology and Microbiology. 2020

Mixed fungal infections– Epidemiology

Blood Mucorales PCR to track down *Aspergillus* and Mucorales co-infections in at-risk hematology patients: A case-control study

Robina Aerts[1,2*], Sien Bevers[3], Kurt Beuselinck[4], Alexander Schauwvlieghe[5], Katrien Lagrou[2,4] and Johan Maertens[2,3]

- N = 46 (2 proven, 31 probable, 11 possible)
- Mucorales PCR positive in 4 cases of IA (8.7%) - probable
  - Controls (no IA) – Mucorales DNA detected in 2 but only + in 1 (Cycle threshold median 32.5)
- Clinical significance remains unclear, mortality was not different between the cases*

  *all 4 cases treated with drugs with well-known activity against Mucorales)

Aerts et al. Frontiers in Cellular and Infection Microbiology. 2022.

Mixed fungal infections– Epidemiology

Quantitative PCR (qPCR) Detection of Mucorales DNA in Bronchoalveolar Lavage Fluid To Diagnose Pulmonary Mucormycosis

Emeline Scherer,[a,b] Xavier Iriart,[c,d] Anne Pauline Bellanger,[a,b] Damien Dupont,[e,f] Juliette Guitard,[g,h] Frederic Gabriel,[i] Sophie Cassaing,[c,j] Eléna Charpentier,[c,d] Sarah Guenounou,[k] Murielle Cornet,[l] Françoise Botterel,[m] Steffi Rocchi,[a,b] Ana Berceanu,[n] Laurence Millon[a,b]

[a]Laboratoire de Parasitologie-Mycologie, Centre Hospitalier Universitaire, Besançon, France

- N = 374 total -> 24 positive BALf PCR
- Mixed infection with Aspergillus 6/24 (25%)
  - Only 1/6 detected using culture method

Sherer et al. Journal of Clinical Microbiology. 2018

Mixed fungal infections– Epidemiology

ORIGINAL ARTICLE

WILEY mycoses

Mixed mold pulmonary infections in haematological cancer patients in a tertiary care cancer centre

Eleni E. Magira[1,2] | Ying Jiang[1] | Minas Economides[1] | Jeffrey Tarrand[3] | Dimitrios P. Kontoyiannis[1]

- 1156 patient with HM and fungal pneumonia = Only 27 (2%) with mixed mold pulmonary infections
- Co-infections: Aspergillus spp (>1), with mucor, fusarium , scedosporium, paecilomyces.
- Outcome not statistically different compared to IPA (*Aspergillus fumigatus*)

Magira et al. Mycoses. 2018

Mixed fungal infections– Epidemiology

ORIGINAL ARTICLE

WILEY mycoses

Isavuconazole for treatment of invasive fungal diseases caused by more than one fungal species

Francisco M. Marty[1] | Oliver A. Cornely[2] | Kathleen M. Mullane[3] | Luis Ostrosky-Zeichner[4] | Rochelle M. Maher[5] | Rodney Croos-Dabrera[5] | Qiaoyang Lu[5] | Christopher Lademacher[5] | Ilana Oren[6] | Anne-Hortense Schmitt-Hoffmann[7] | Michael Giladi[8] | Galia Rahav[9] | John R. Perfect[10]

[1]Division of Infectious Diseases, Brigham and Women's Hospital, Boston, MA, USA

- N = 15 patients included
- Treated with Isavuconazole
- Comparable all-cause mortality rate in patients with mixed fungal infections vs with mucormycosis only

Marty et al. Mycoses. 2018

Mixed fungal infections– Take home points

- Aspergillus most common pathogen a/w mixed infections.
- Mixed infections prevalence rate: 20-25% (PCR era)
- Previous literature: mixed infections 4% based on conventional microbiological procedures (culture and microscopy)
- Comparable mortality (one vs multiple mold infections)
  - Could be explained by the widespread empiric use of broad spectrum antifungal therapy
- Case reports: severe infections of more than one mold have been reported.
- Caveats: not a lot of autopsy reports, so unclear clinical significance.

Sherer et al. Journal of Clinical Microbiology. 2018
Millon et al. Clinical Microbiology and Infection. 2022
Garcia-Vidal et al. CID. 2008

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