A Sunday On-Call Surprise: An Unusual Case in a Lung Transplant Patient

West Coast TID Society Conference

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Infectious Diseases Division

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Disclosures

None

Chief Complaint/History of Present Illness

- ** y/o * with h/o bilateral orthotopic lung transplant (BOLT) on ****/2023
  - Shortness of breath, DOE, sore throat, productive cough with whitish to brownish sputum, and chills for 3 days.
  - Nonspecfiic chest and diffuse abdominal pressure for one day.

- Presented to OSH for acute hypoxic respiratory failure with RLL consolidation/atelectasis, started on Vanco/zosyn, then transferred to our hospital on ****/24.

Lung transplant background

- BOLT on *****/2023; induction with basiliximab
- Etiology: MCTD (SLE and scleroderma)-ILD (MMF/prednisone)
- CMV +/+, EBV +/+, toxoplasma ?/+
- RLL transbronchial biopsy (*** 2024)
  - ACR A1: Prednisone taper (started with 40mg twice daily, 10mg daily on *****/24)
  - GMS with clusters of fungal hyphae (BAL culture with *A. fumigtus*) s/p voriconazole for 6 months (until 1 mo prior to admission)

- IS: Tacrolimus (goal 8-10), Imuran (held), Prednisone 10mg daily
- Prophylaxis: bactrim, valganciclovir, BOS prophylaxis with azithromycin.

- Neutropenia (ANC 210/μL): filgrastim starting late October 2024

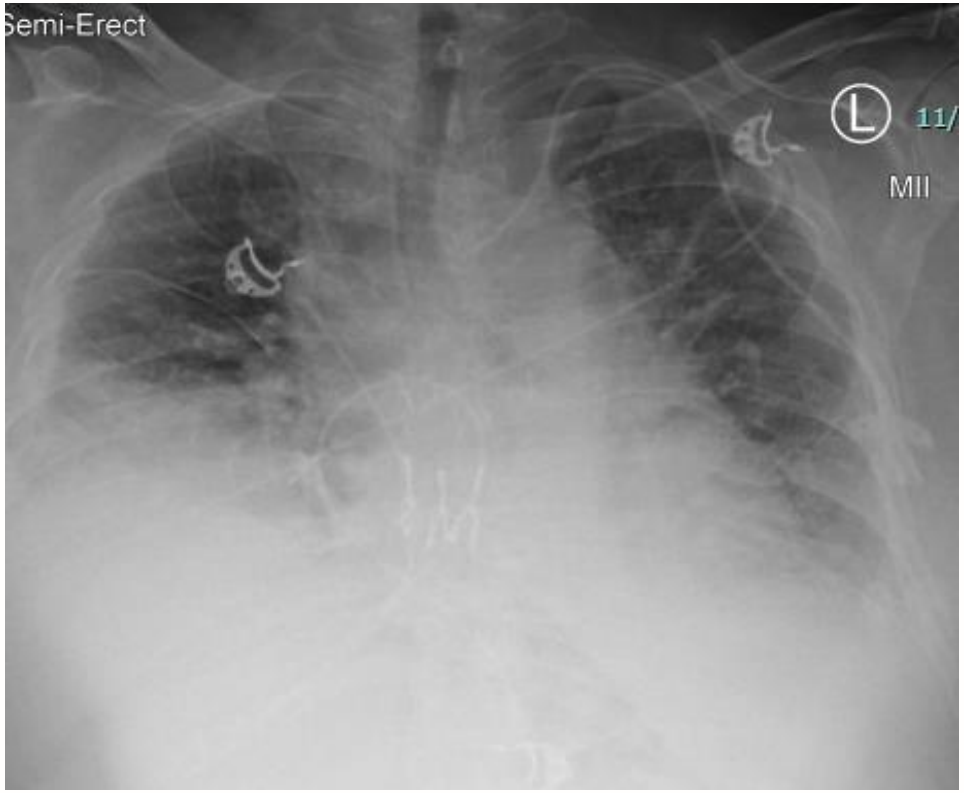
Medical, Surgical, Allergy, and Social History

- Medical history:
  - MCTD-ILD, HTN, pulmonary HTN, chronic rhinosinusitis, GERD, gastritis, hyperlipidemia.
  - CMV viremia (9/**/24-10/**/24): ganciclovir IV and cytogam
- Surgical history:
  - BOLT on ******2023
  - Sigmoidectomy (detalis unknown)
- No known drug allergies
- Social history:
  - Born/raised in Honduras; moved to the US in 2007; lived in a mobile home with *** husband and a ** year-old daughter (**********, CA -- agricultural sector).
  - Worked in the agriculture fields until 5 years prior to admission
  - No smoking, drinking or substance use
  - No pets or recent animal exposure, no recent travel or known sick contacts.

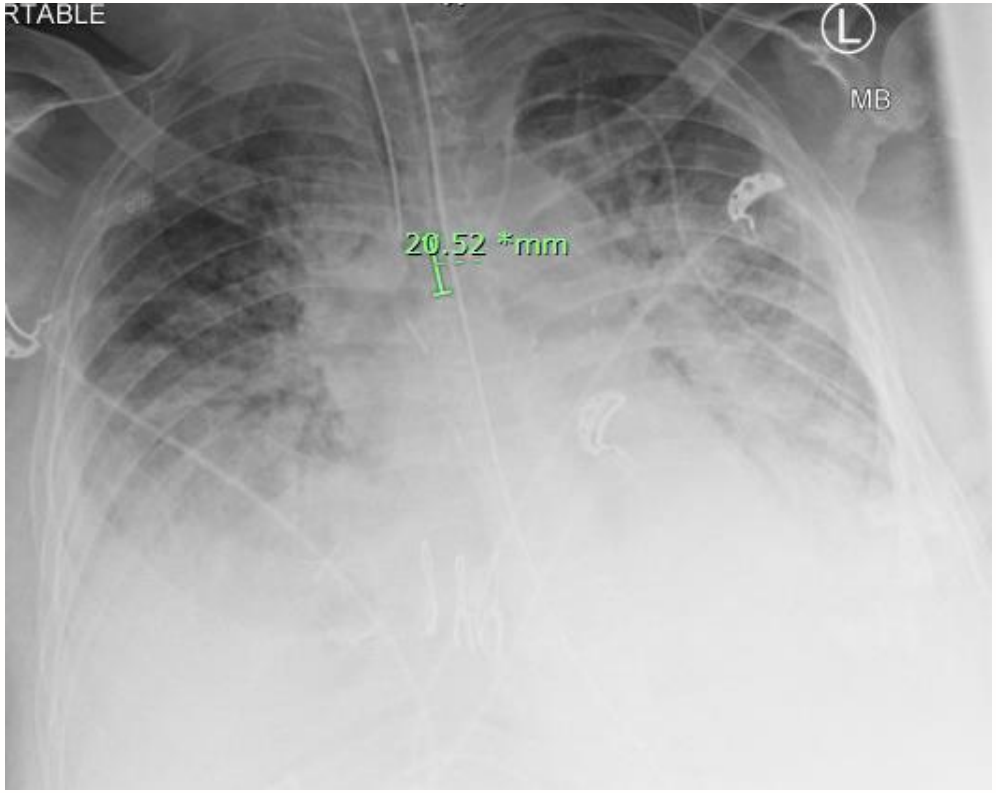
Hospital course

- (d1) T 37.9C, tachycardic HR 100s, tachypneic RR 20s, moderate distress with increased work of breathing on admission. ANC 680 /μL, ALC 880 /μL.
  - NP swab for respiratory pathogen panel positive for rhinovirus/enterovirus PCR

- (d3) T 38.7C, intubated for worsening respiratory status (CXR with worsening airspace opacities).
  - Bronchoscopy/biopsy - intact anastomosis, thick mucus secretion at Lt main carina
    - Patho H&E: numeous histicytes/inflammatory cells, and blood.
    Gram stain, AFB and GMS stains negative.
    - BAL:Respiratory culture (normal respiratory flora). AFB culture, fungal culture, legionella cultures/galactomannan/aspergillus PCR negative, positive for rhinovirus/enterovirus PCR
  - Serum CMV PCR, Cocci Ab, cryptococcal Ag, B-D glucan, galactomannan negative. Urine&serum Histoplasma Ag negative.
  - Vancomycin IV, meropenem IV, levaquin



Admission (11/28/24)



(11/30/24)

ARDS: viral component vs. early rejection, steroid pulse (methylprednisolone 250mg x1 ([redacted]), 500mg Q12hr ([redacted]-[redacted]) taper).

Hospital course

(d4) Septic shock, AKI with initiaiton of CRRT. Voriconazole added for empiric fungal pneumonia coverage for worsening oxygenation.

**blood cultures drawn every 1-3 days since admission (e.g. shock, fever), catheter Δ*

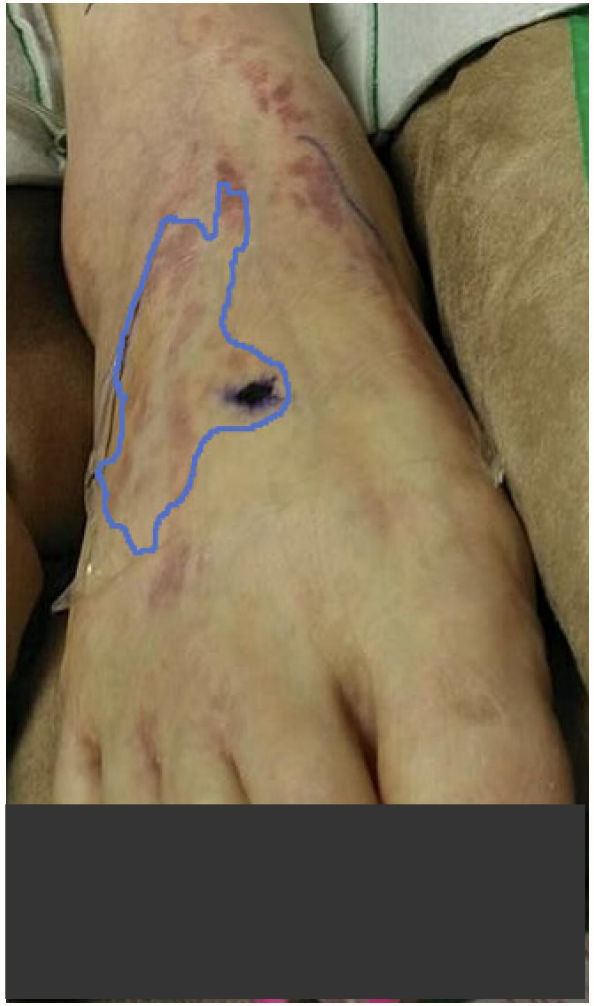
(d6) "Duskiness and ischemic changes on feet and hands".

(d12) "Mottled skin changes of upper arms and feet"

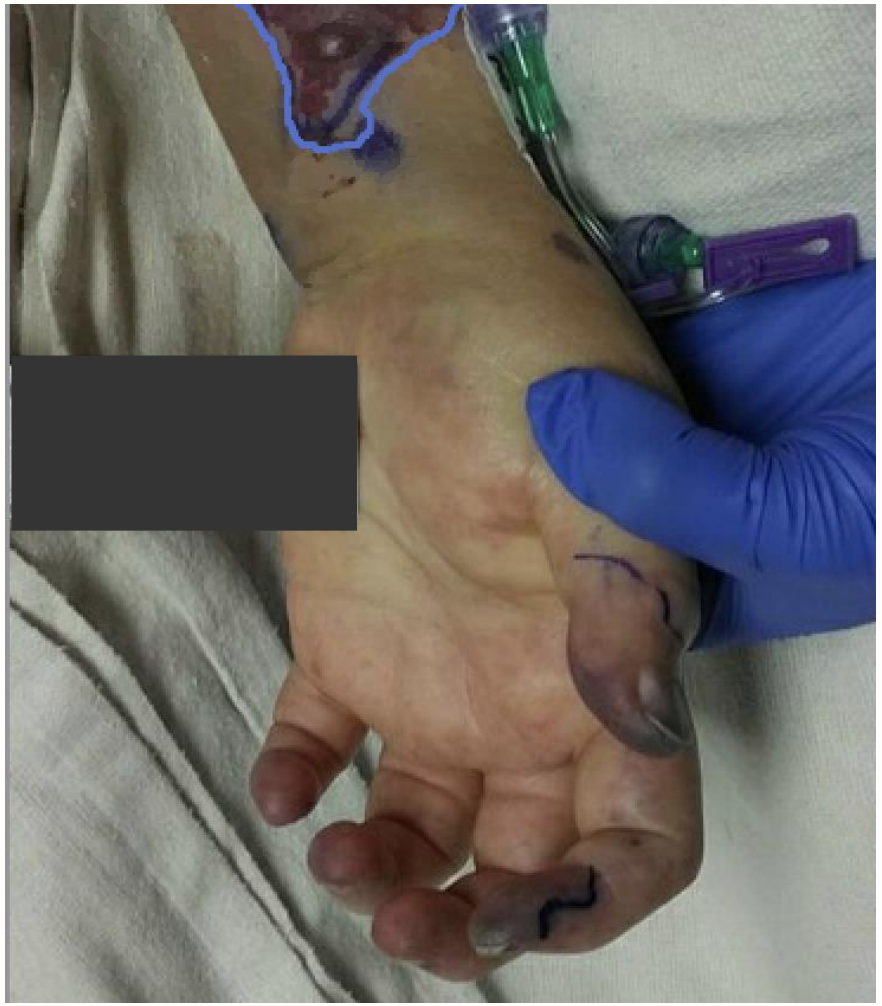
(d14) "skin lesions are spreading", dermatology consulted.

"Petechial macules" on plantar/dorsal feet and ankles; "dusky purpuric patches" on fingertips; "Retiform violaceous plaques with hemorrhagic crusting and overlying bullae" on arms and inferior breasts.

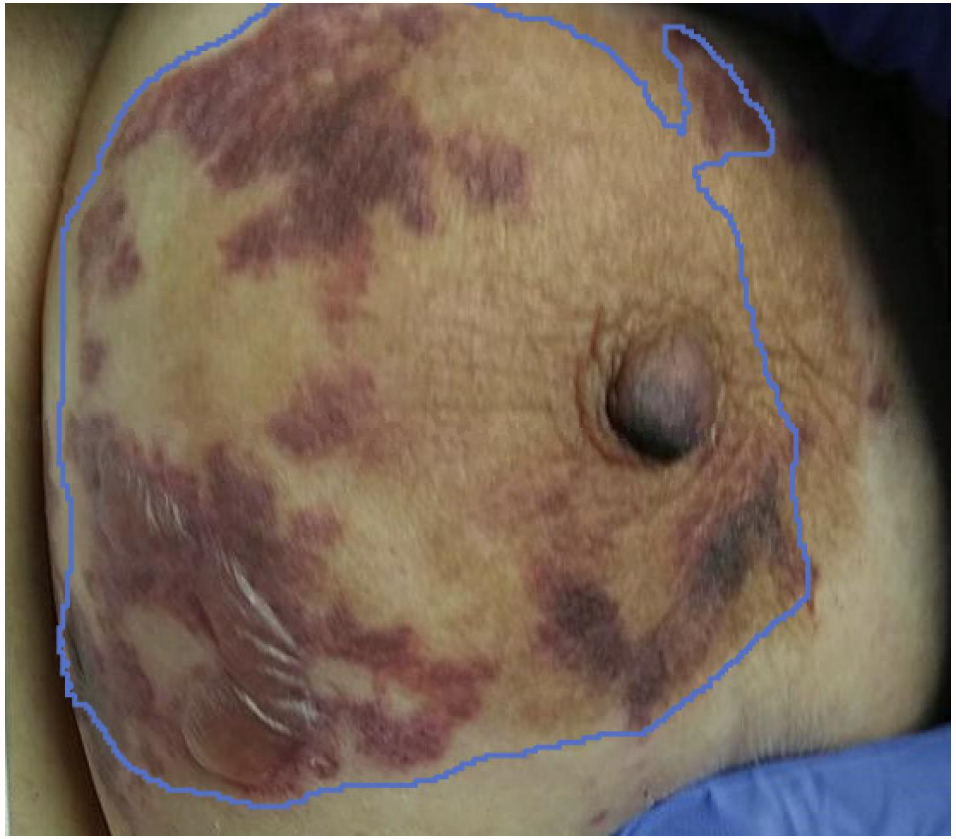
"Retiform purpura"– vasculitis, calciphylaxis, angioinvasive organisms, vs. thrombotic occlusive phenomenon.



d13; Rt foot



d13; Lt hand/forearm



d17; Lt breast

Punch bx x2 from Lt forearm: thrombotic vaso-occlusive process with proteinaceous debris favoring DIC/Coagulopathy; Gram stain and PAS fungal stain negative

Question 1: Blood cultures (d 12) are growing “Mold”. What mold is it?

(a) *Fusarium spp*.
(b) *Scedosporium spp.*
(c) *Lomentospora prolificans*
(d) *Aspergillus spp.*
(e) *Mucor spp.*

Question 2: “Mold growing in the blood culture” What is the next step in the workups?

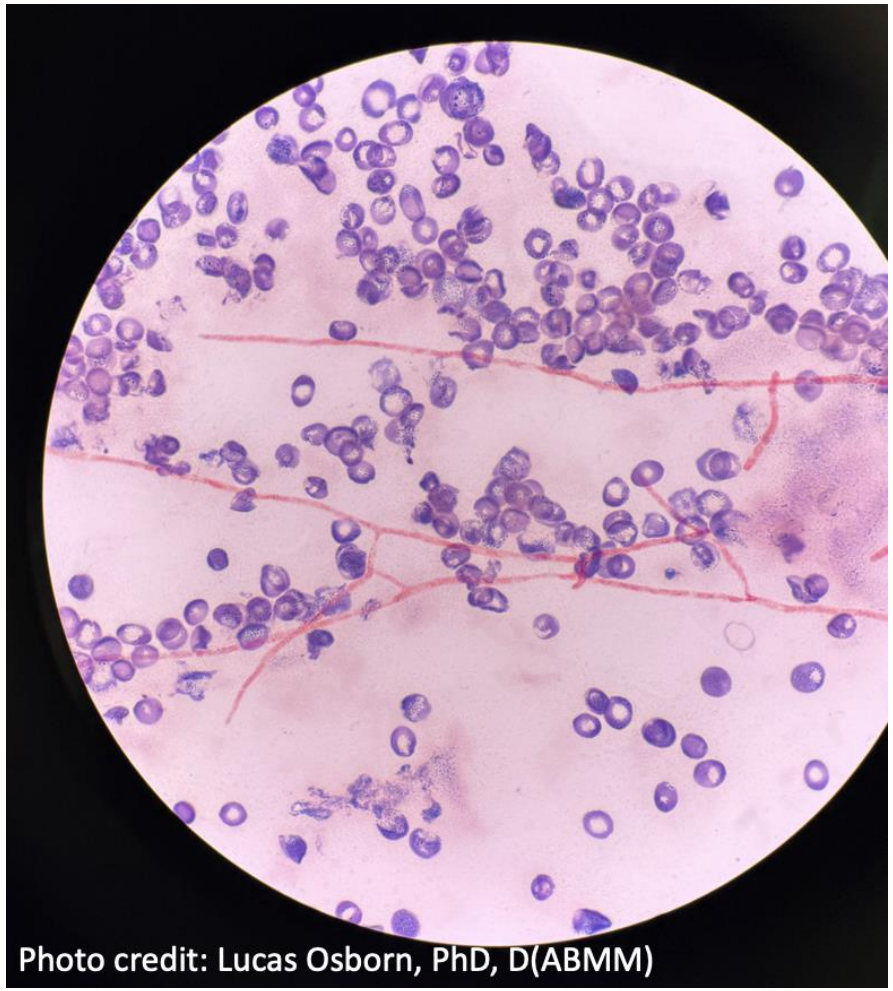
(a) Ophthalmology consult for dilated eye exam
(b) Repeat blood cultures
(c) CT or MRI of brain, sinuses, and/or orbits
(d) TTE/TEE to r/o endocarditis

Hospital course

- LP (d16): no opening pressure, WBC 3, protein 46, glucose 107 (fungal and AFB cx negative)
- Chest CT with mild interval increase in Lt hilar and bibasilar consolidation and GGO in the LUL. Bronchoscopy (d16): intact anastomosis, mild inflammed B/L distal airway, small mucus pluggin in LUL → GMS fungal hyphae/pseudohyphae, BAL culture growing "mold"
- TEE (d19): TV with a small mobile hyperechoic density (vegetation)
- CT of head/sinuses, nasal endoscopy (d20): no evidence of invasive fungal sinusitis
- Ophthalmology exam (d23): Rt temporal retinal whitening → Rt total retinal whitening compatible with fungal chorioretinitis. s/p vitreal tap and voriconazole injection→ vitreal culture positive with "mold"

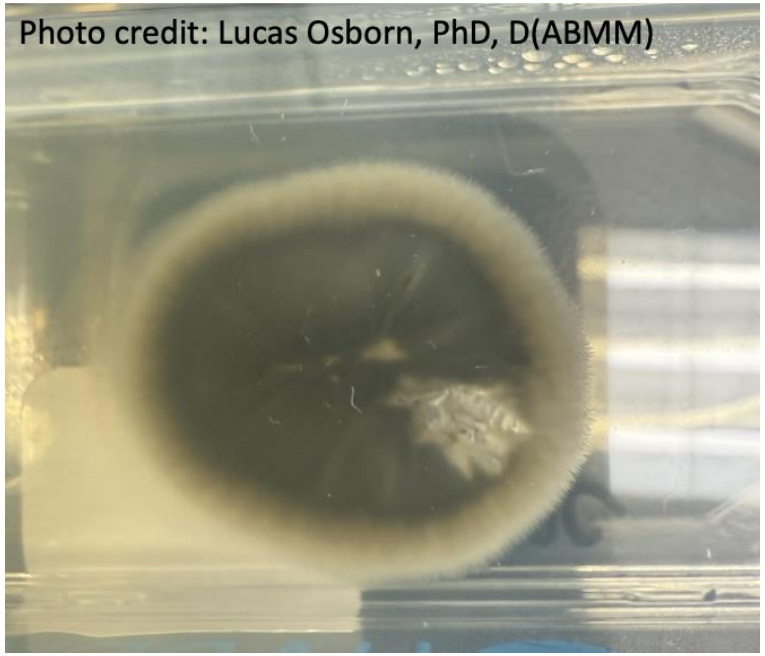
Lomentospora prolificans

MALDI-TOF/MS : L. prolificans



Gram stain in the blood culture (x100):
“septated hyphae and conidia”

Colony morphology:
“olive gray with white mycelial tufts”
on Sabouraud dextrose agar



Reverse colony
on Sabouraud dextrose agar

Question 3: You are consulted for “Disseminated infection with *Lomentospora prolificans”, w*hat combination therapy would you start with ?

(a) Ambisome + micafungin
(b) Ambisome + micafungin + voriconazole
(c) Voriconazole + ambisome
(d) Voriconazole + terbinafine
(e) Voriconazole + terbinafine + another agent

Question 4:
what investigational drug is active against *L. prolificans* ?

(a) Fosmanogepix
(b) Olorofim
(c) Ibrexafungerp

Mold-positive blood cultures: French RESSIF surveillance database (2012-2022)

Total 80 cases during the 10-year:

- *Fusarium* spp. is the most common (67.5%)
- *Lomentospora prolificans* (10%): 2nd most common
- *Aspergillus* spp., *Mucorales, Trichoderma* spp. (5% each)

- **Overall, hematological malignancy (HM) 70%** [43% with allo-HSCT], GI 13%, SOT 5%.
- **Neutropenia** (49%)

Tala-Ighil et al. Clin Infect Dis 2025 Vol. 80 Issue 3

Mold-positive blood cultures: French RESSIF surveillance database (2012-2022): *Tala-Ighil et al. Clin Infect Dis 2025 Vol. 80*

Characteristic	*Fusarium* spp (n=54)	*Lomentospora prolificans* (n=8)	*Trichoderma* spp (n=4)	Mucorales (n=4)	*Aspergillus* spp (n=4)
Medical history	HM (72%); SOT(1.9%); neutropenia (56%); ICU (15%)	HM (88%); SOT (12%); neutropenia (50%); ICU (63%)	HM (75%); SOT (0%) neutropenia (50%); corticosteroids (100%)	HM* (50%); SOT (25%); Neutropenia (0%) ICU (75%); corticosteroids (50%)	HM* (75%); SOT (0%) Neutropenia (50%); ICU (100%)
Antifungal preexposure	46%	63%	25%	0%	25%
Organ involvement	Lung (40%); Skin (51%); Lung+skin (26%)	Lung (86%); Skin (43%); Lung+Skin (43%)	Lung (25%) Skin (0%) Lung+Skin (0%)	Lung (50%) Skin (25%) CNS (25%) Lung+Skin (0%)	Single localization (100%) Lung (25%), Skin (25%), CNS (25%)
Mortality at 90d	43%	100%	50%	75%	100%
Time to 1st (+), median (hours)	~77	62.7	65.1	38.4	63

HM. Hematologic malignancy; HM* -no allogeneic HSCT; Neutropenia < 500 cells/µl for 10d+

Mold-positive blood cultures:
French RESSIF surveillance database (2012-2022)

Independent predictors of mortality compared to *Fusarium* spp. (multivariable analysis):

- *L. prolificans* (OR 33.3)
- *Aspergillus spp* (OR 14.2)
- Corticosteroid exposure (OR 7.85)

Central venous catheter (CVC) involvement was rare. CVC culture without organ involvement, mainly *Fusarium* spp molds (5/6). Only 1 Mucorales fungemia.

***Fungemia itself could be a better indicator of dissemianted disease than CVC associated infection.**

Tala-Ighil et al. Clin Infect Dis 2025 Vol. 80 Issue 3

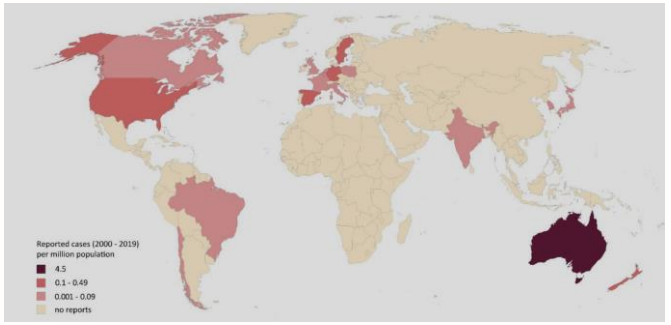
Invasive phaeomycosis
Invasive lomentosporiosis
Lomentospora prolificans infection

- Formerly known as : *Scedosporium prolificans*; *Scedoporium inflatum*
- Mode of entry: Initial lung involvement followed by dissemination to skin. Direct inoculation into the skin followed by dissemination.
- Skin manifestation: “erythematous non-pruritic skin nodules +/- a necrotic center”, “necrotic papule, hemorrhagic bullae, ecchymoses”, “Solitary ulcers, infiltrative erythematous or suppurative plaques and nodules”
- CT: nodular consolidation or infiltrates without cavitation. Halo signs or air crescents were not reported

Tala-Ighil et al. Clin Infect Dis 2025 Vol. 80 Issue 3
Neoh et al. Clin Microbiol Rev 2024 Vol. 37
Larone's Medically Important Fungi: A Guide to Identification, 6th Edition

Lomentospora prolificans infection

Ramirez-Garcia et al. Med Mycol 2018 Vol. 56



- Polluted soils/waters, Agricultural areas, urban parks and playgrounds, warm arid climates with neutral PH
- Australia, southwestern USA (California), Spain, France, Germany, Portugal, Japan, Korea. etc.
- Trauma-associated infections, near-drowning episode in healthy individuals
- Pulmonary colonization in CF or lung disease.

- Conidiation in host tissue — promotes dissemination and explains rapid progression of disease
- Sabouraud dextrose agar; Sce-Sel+ media; MALDI-TOF/MS, DNA Sequencing

Invasive *Lomentospora prolificans and Scedosporium* Infections in Australia : 2005-2021 (6-center, 61 cases). *Neoh et al. Open Forum Infect Dis 2023 Vol. 10*

Characteristic	*L. prolificans* (37 cases)	*Scedosporium* (24 cases): *S. apiospermum* complex (20) *S. aurantiacum* (4)
Hematologic malignancy	81.1%	33.3%
allo-HSCT	29.7%	12.5%
Renal transplant	0	20.8%
Cardiothoracic transplant*	8.1%	4.2%
Baseline neutropenia	70.3%	16.7%
Prolonged neutropenia	62.2%	16.7%
Chemotherapy	59.5%	16.7%

* Not statistically significant; prolonged neutropenia-neutropenia < 500 cells/µl for 10d+

Invasive *Lomentospora prolificans and Scedosporium* Infections in Australia : 2005-2021 (6-center, 61 cases). *Neoh et al. Open Forum Infect Dis 2023 Vol. 10*

Characteristic	*L. prolificans* (37 cases)	*Scedosporium* (24 cases): *S. apiospermum* complex (20) *S. aurantiacum* (4)
Disseminated infection	73%	8.3%
Blood	62.2%	0
CNS	29.7%	8.3%
Lung	78.4%	37.5%
Skin/Soft tissue	13.5%	37.5%
Median antifungal days	10.5 (vori+terbinafine 96.8%)	156 (vori 62.5%)
1-month mortality	70.3%	4.2%
Median time to death (days)	6	62.5

Scedosporium/*Lomentospora prolificans*: 80 transplant patients (13 from 5 centers, 67 from literature) *Husain et al. Clin Infect Dis 2005 Vol. 40*

- **Scedosporium 76%/*Lomentospora prolificans* 24%**
- ~25% of non-Aspergillus mold infections in SOT
- Voriconazole trends toward better survival.

Scedosporium/*Lomentospora prolificans*: 80 transplant patients (13 from 5 centers, 67 from literature) *Husain et al. Clin Infect Dis 2005 Vol. 40*

Characteristic	SOT (n=57)	HSCT (n=23)	Hematologic malignnacy (n=69)
Prior antifungal ppx	20%	64%	23%
Disseminated	55%	69%	86%
Neutropenia	13%	67%	90%
Mortality	57%	68%	76.8%
S. apiospermum	83%	60.9%	24.6%
L. prolificans	17%	30.1%	75.4%

Treatment: *L. prolificans*

Global guideline *Hoenigl et al. Lancet Infect Dis 2021 Vol. 21*

- Surgery (debridement, enucleation, vitrectomy)
- First-line: voriconazole plus terbinafine (despite high in vitro MICs) +/- other antifungals (global guidline ECMM/ISHAM/ASM)

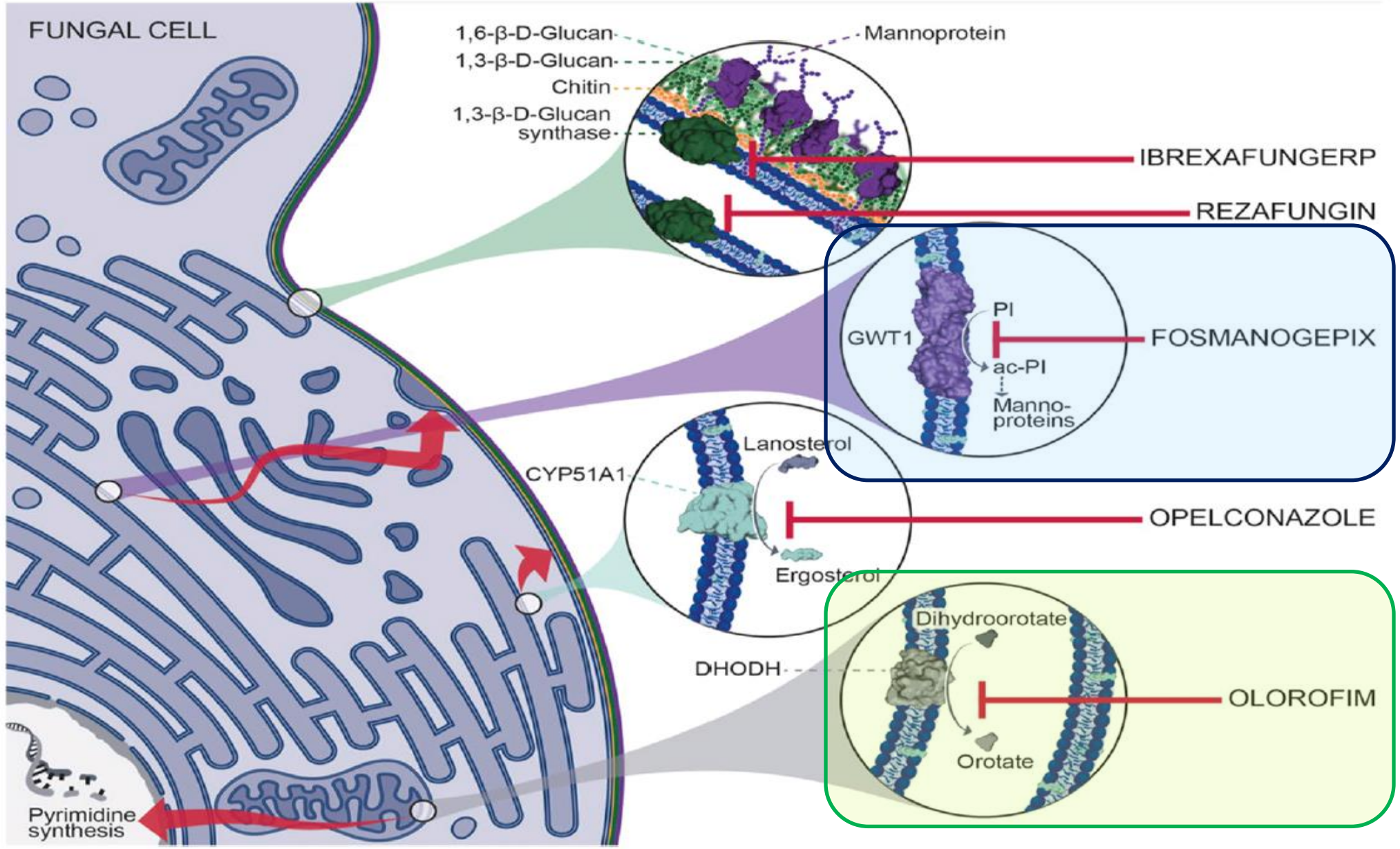
- Analysis of 41 patients with invasive *L. prolificans* from **Fungiscope®** registry (2008-2019, 8 countries) *Jenks et al. Clin Microbiol Infect 2020 Vol. 26*
  - 28-day survival (62.5% combination vs. 0.25% monotherapy).
  - Vori+terbinafine associated with higher rates of treatment success (63% vs. 29%), higher median survival 150d vs. 17d.

- Literature and **Fungiscope® (2000-2017, 56 cases)** *Seidel et al. Crit Rev Microbiol 2019 Vol. 45*
  - Overall mortality: voriconazole vs. other antifungals (52.6% versus 68.8%). Vori + terbinafine vs. vori, 42d mortality not different.

Treatment: *L. prolificans*

- UCSD (2014-2017): 8 cases. All three patients with monotherapy did not survive at 180d. Four/Five patients with combination survived (Vori+Terbinafine, V+T+Micafungin, V+T±M, V+M survived; V+AmB died).
  Jenks et al. Int J Antimicrob Agents 2018 Vol. 52

Hoenigl et al. Drugs 2021 Vol. 81



Olorofim (F901318): orotomide

- Olorofim (F901318): no activity against *candida, cryptococcus,* Mucorales group. Variable activity against *Fusarium*. Activity against *Histoplasma, Cocci, Scedosporium* spp., *L. prolificans.*

- Breakthrough therapy designation (FDA): treatment of invasive mold infections with limited or no treatment options (Nov 2019), CNS cocci refractory to SOC (Oct 2020)

- Orphan drug designation (2020)
- Qualified ID product designation (June 2020): treatment of invasive aspergillosis/scedosporiosis/lomentosporiosis/scopulariopsis/fusariosis, coccidioidomycosis

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Olorofim (F901318): orotomide

- Phase IIb open label (FORMULA-OLS, NCT03583164, n=53) completed: interim result in IDWeek 2022.

Successful EORTC-MSGERC overall response (complete or partial based on clinical + radiologic + mycologic improvement d42/d84): 47%/42% (IA, n=53), 53%/53% (*L. prolificans*, n=17), 55%/36% (*Scedosporium*,n=11), 50%/50% (other molds, n=8)

Hoenigl et al. Drugs 2021 Vol. 81
OFID 2022:9 (Suppl 2). Oral abstract

Successful cases: Olorofim (F901318): orotomide

- Three cases of successfully treated disseminated *L. prolificans* infection with olorofim – used either as monotherapy after failure of other treatments or in combination with voriconazole and terbinafine – in patients with T-cell lymphoblastic leukemia, allo HSCT, and a breast implant.

Hoenigl et al. Drugs 2021 Vol. 81
OFID 2022:9 (Suppl 2). Oral abstract
Dong et al. J Ophthalmic Inflamm Infect 2024 Vol. 14

Fosmanogepix (APX001)

- Fast track status by FDA
- Broad-spectrum activity, including *Fusarium, Scedosporium, L. prolificans, cryptococcus, Histoplasma, Cocci*; no activity against *C. Krusei; v*ariable against Mucorales and *Alternaria alternata.*

- Phase 2 NCT04240886(invasive Aspergillus and rare mold)—21 patients. Primary endpoint all-cause mortality at d42 (APX001), 25% vs. 45% other antifungal medications.

- A successfully treated case using Fosmanogepix monotherapy in allo-HSCT patient with PTLD, following failure of combination therapy.

Hoenigl et al. Drugs 2021 Vol. 81
Stanford Univ (disseminated fusariosis), June 12, 2024 West Coast TID
Cobo et al. Diagn Microbiol Infect Dis 2024 Vol. 110

Main takeaways: *L. prolificans*

- Second most common cause of mold-positive blood cultures.
- One of the deadliest mold infections
- Hematologic malignancy, HSCT, SOT, neutropenia.
- Familiar with the skin findings and lung images
- Other systems: Eye, heart, and CNS
- Drugs: combination therapy (voriconazole+terbinafine+another agent)
- Investigational drugs: Olorofim or Fosmanogepix

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