



UMC Utrecht

ECCMID 2018 Grand Rounds



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Case presentation

- 56-year old woman
- Past medical history:
 - (May 2016) Pontine hemorrhage, no residual effects
 - (June 2017) Auto-immune hepatitis with cirrhosis
Child Pugh C
Started on prednisone 60 mg
- **One week after discharge:** Re-admitted because of malaise and dyspnea



At the emergency department

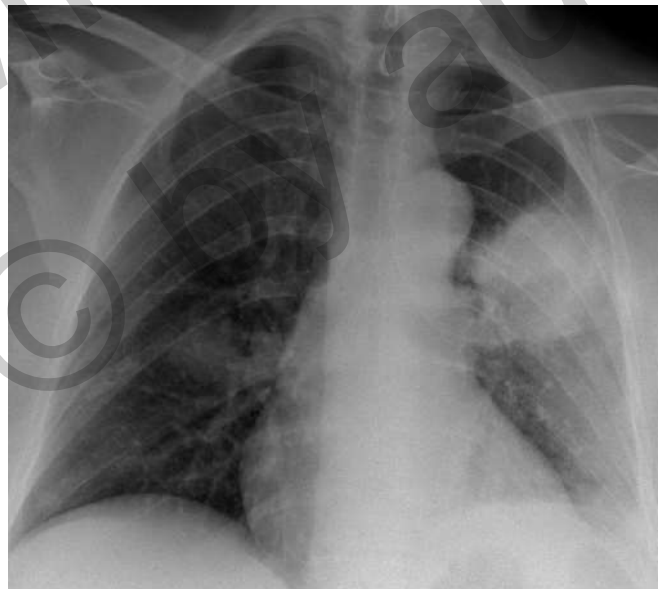
- General malaise
- No fever
- Dyspnoea and non-productive cough
- Been using prednisone for 3 weeks, currently on 50 mg.

- Looks ill
- 97/70 mmHg. Pulse 76/min. T 37.2
- Oxygen saturation 89% breathing ambient air
- Crackles left upper lobe



At the emergency department

- Laboratory:
 - * Normal FBC. C-reactive protein 97 mg/L (<10 mg/L)
 - * Liver enzyme elevations improved. Child Pugh B
- Diagnosis: Pneumonia
- Therapy: Amoxicillin-Clavulanic Acid



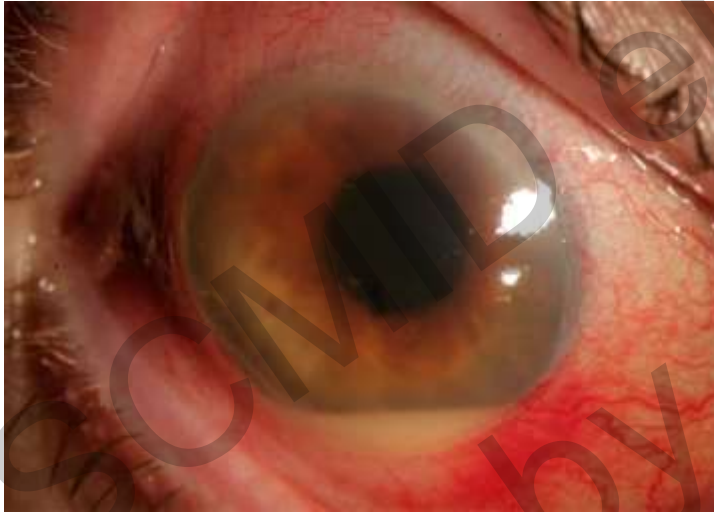
After 3 days...

- After 72 hours broad spectrum antibiotics: Clinically stable but no improvement. C-reactive protein declined to 67 mg/L
- Pneumococcal urinary antigen weakly positive
- Blood cultures: No growth
- No sputum cultures available
- CT-scan: Cavitory pneumonia. No empyema.
- IGRA - *M. tuberculosis*: Indeterminate



After 7 days...

- Amoxicillin clavulanic-acid stopped after 7 days
- Blurred vision left eye



- Endogenous endophthalmitis



Panel Discussion

- Differential diagnosis & Management

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- Endogenous endophthalmitis
 - * Ceftazidime
 - * Vancomycin
 - * Vancomycin intravitreal
 - * Ceftazidime intravitreal
- Bacterial culture ocular fluid: Negative
- At 12th day of admission:
 - * Clumsiness of right hand & difficulty swallowing



After 12 days...



Any modifications in empiric antibiotic therapy?



- Treatment modified
 - * Ceftriaxone
 - * Metronidazole
 - * Vancomycin intravitreal
 - * Ceftazidime intravitreal

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Summary

- Cirrhotic patient with a relatively short course of steroids
- Pulmonary, cerebral and ocular involvement
- Poor response to broad spectrum antibiotic therapy

- All cultures: Negative
- Pneumococcal urine antigen test: Weakly positive
- Echocardiogram: No signs of endocarditis

- Broncho-alveolar lavage: Not performed
- CSF examination: Not performed

- Transfer to academic hospital for further evaluation



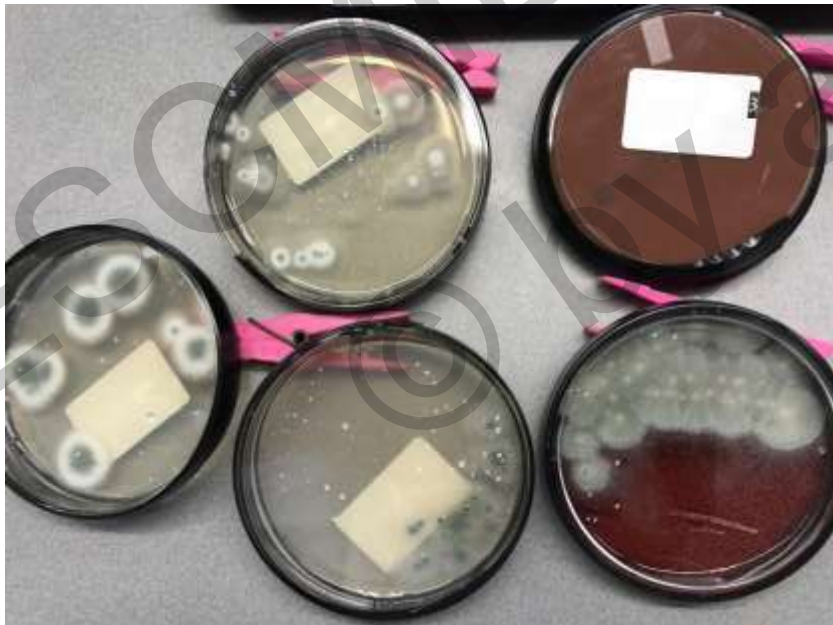
Differential diagnosis & management

- Infectious Disease differential diagnosis
 - *Tuberculosis
 - *Invasive fungal infection
 - *Nocardiosis
 - *Multi-resistant bacterial infection
- All antibiotics were stopped
- Mycobacterial blood cultures
- Broncho-alveolar lavage for cultures + Galactomannan
- New ocular fluid puncture



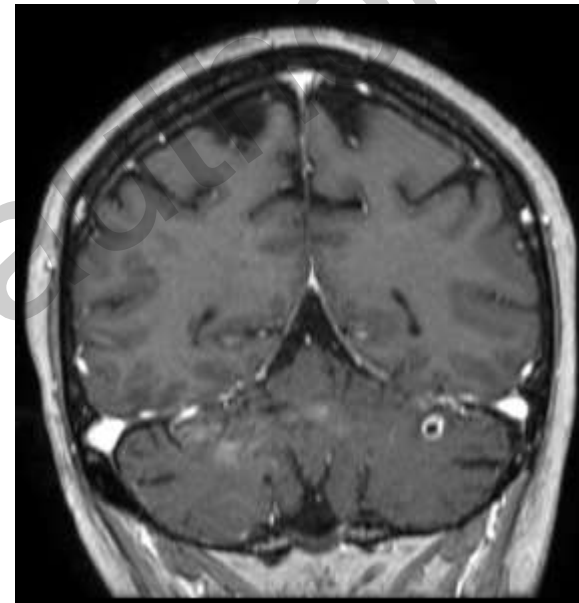
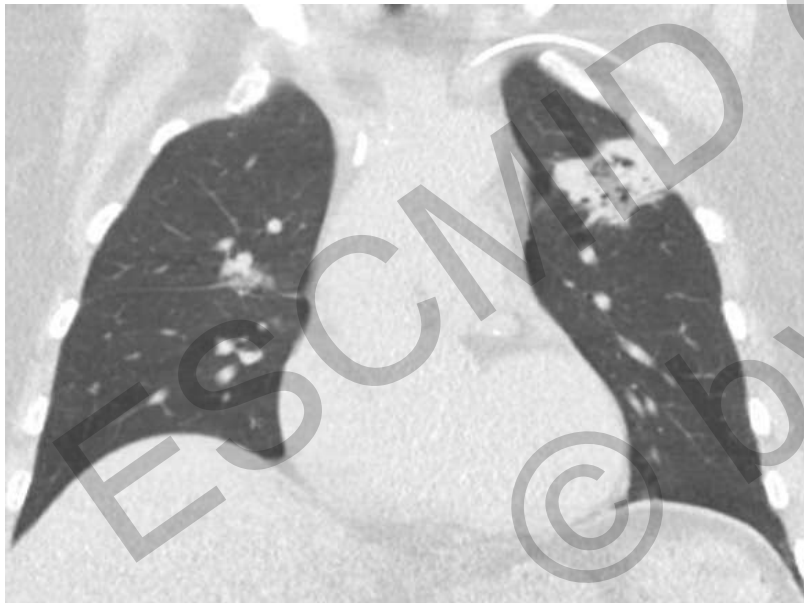
Test results

- Broncho-alveolar lavage fluid:
 - * Bacterial cultures: Negative. PCR *M. tuberculosis* & AFB both negative
 - * *Candida albicans* 10 – 100 cfu. Other fungal cultures negative.
 - * Galactomannan: 2.53/positive (<0.5)
- Ocular fluid cultures: *Aspergillus fumigatus*



Diagnosis

- Disseminated Invasive Aspergillosis
- Cerebral, pulmonary & ocular localization



Therapy?

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Therapy

- Considerations:
 - * Need for good CNS penetration
 - * (Relative) contra-indication azole because of cirrhosis

Table 4.5.7.1 Overview of number of *A. fumigatus* culture-positive patients and frequency of azole resistance in 5 UMCs in 2013 to 2015.

| | 2013 | | 2014 | | 2015 | |
|--------------|--------------------|---|--------------------|---|--------------------|---|
| | #patients screened | #patients with confirmed azole resistant isolates (%) | #patients screened | #patients with confirmed azole resistant isolates (%) | #patients screened | #patients with confirmed azole resistant isolates (%) |
| ErasmusMC | 231 | 10 (4.3) | 265 | 10 (3.8) | 22 | 7 (31.8)* |
| LUMC | 99 | 19 (19.2) | 113 | 15 (13.3) | 141 | 23 (16.3) |
| Radboudumc | 123 | 6 (4.9) | 143 | 7 (4.9) | 145 | 12 (8.3) |
| UMCG | 194 | 16 (8.2) | 191 | 18 (9.4) | 225 | 15 (6.7) |
| VuMC | 113 | 8 (7.1) | 104 | 9 (8.7) | 89 | 14 (15.7) |
| Total | 760 | 58 (7.6) | 814 | 59 (7.2) | 600 | 64 (10.7)** |

* *A. fumigatus* isolates from 22 ICU and hematology patients were screened for azole resistance.

** Based on four centers where screening of unselected isolates took place.



Therapy

- 4.8.17: Start Liposomal Amphotericin B (LAB) 5 mg/kg
- 4.8.17: Intravitreal Amphotericin B
- 7.8.17: PCR TR34/L98H: Negative, azole resistance is unlikely.
- Start voriconazole in reduced dosage (50%) in addition to LAB
- 10.8.17: Severe hallucinations
- 11.8.17: VCZ trough concentration: 1.4 mg/L (2.0 – 5.0). VCZ stopped.



What to do next?

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Therapy

- 15.8.17: Start Isavuconazole 200 mg t.i.d. loading dose for 48 hours, followed by 200 mg once daily
- 22.8.17: *A. fumigatus* susceptible to azoles, switch to isavuconazole monotherapy

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Follow-up at 9 months

- Clinically stable. No side effects of isavuconazole therapy.
- Regression of the pulmonary and cerebral lesions
- Permanent loss of vision left eye
- Stable liver cirrhosis – using 10 mg prednisone



Take Home Messages

- Neutropaenic patients are not the sole risk group for invasive aspergillosis
- Invasive diagnostics should not be withheld when a infection in immunocompromised patients is suspected
- Isavuconazole seems a good alternative in case of voriconazole toxicity or contra-indications

