DESC Maladies infectieuses et Tropicales

INFECTIONS FONGIQUES ORL

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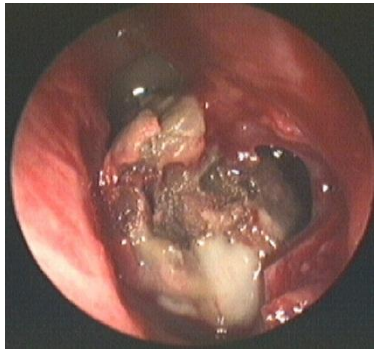
Liens d’intérêt: Benjamin Verillaud

Consultant	Medtronic, Sanofi-Genzyme
Invitation à des congrès	Amplifon, Medtronic, Sanofi-Genzyme
Orateur rémunéré	Amplifon, Collin, Mylan, Medtronic, Sanofi-Genzyme, GSK

PLAN

- Otites fongiques :
  - Otites externes non invasives
  - Otites fongiques invasives

- Sinusites fongiques
  - Balle fongique
  - Sinusite fongique allergique
  - Sinusites fongiques invasives

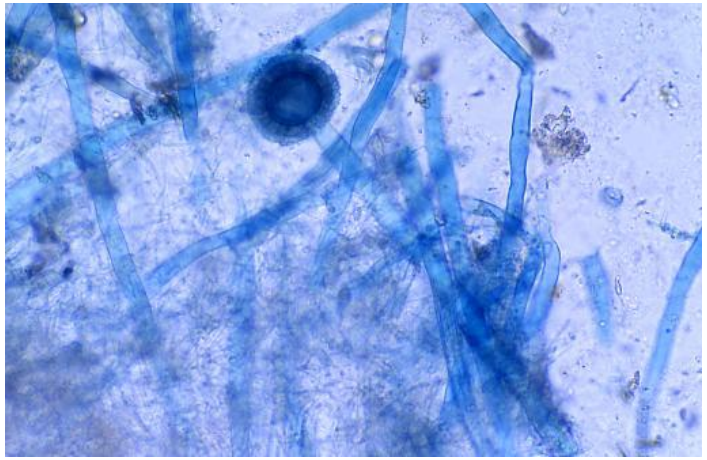


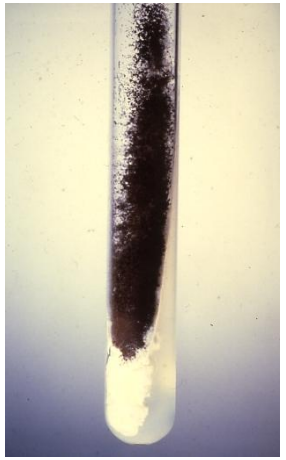
OTITES FONGIQUES

INFECTIONS FONGIQUES EN OTOLOGIE : GÉNÉRALITÉS

- Deux grands cadres nosologiques :
  - Pathologie cutanée du conduit , non invasive = **“otomycose”**
  - **Mycose invasive : patient diabétique/immunodéprimé… le plus souvent**

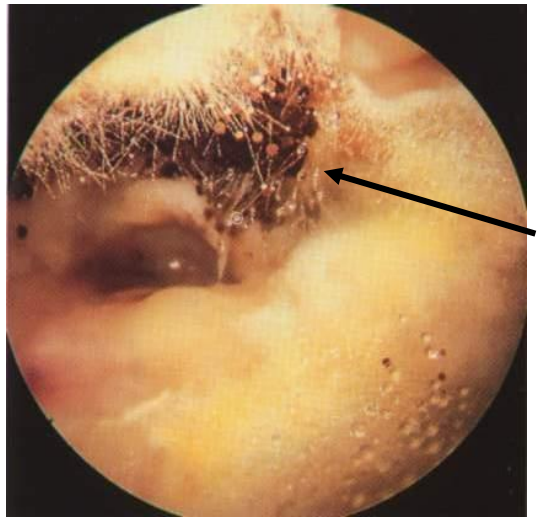
- Essentiellement dues à ***Aspergillus niger et Aspergillus fumigatus***…(quasi-certain quand des têtes sont visibles)





OTOMYCOSE

- Fréquente++ notamment en période estivale et chez la femme enceinte
- Infection superficielle du CAE cutané
- **Diagnostic clinique : otalgie, otorrhée… et otoscopie**
- **Souvent associée à une otite externe bactérienne (5 à 30% des cas)**, ou à une otite moyenne avec otorrhée (cholestéatome, otite chronique non cholestéatomateuse avec perforation tympanique)
- Prélèvements microbiologiques :
  - Mycologique : dans le conduit (+ biopsie seulement si doute sur le caractère invasif)
  - Bactériologique ++



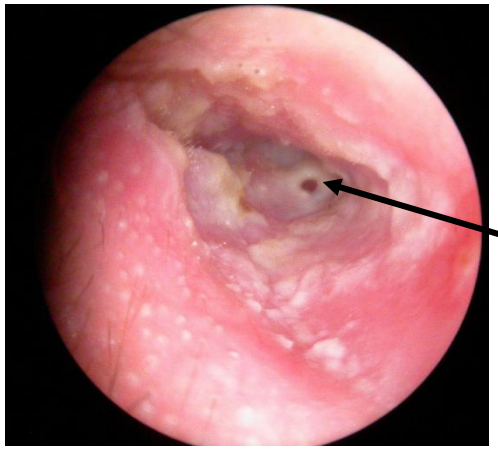
Otorrhée colonisée à *Aspergillus niger*

Patterson et al. Clin. Infect. Dis. 2016;63:433–442.

OTOMYCOSE

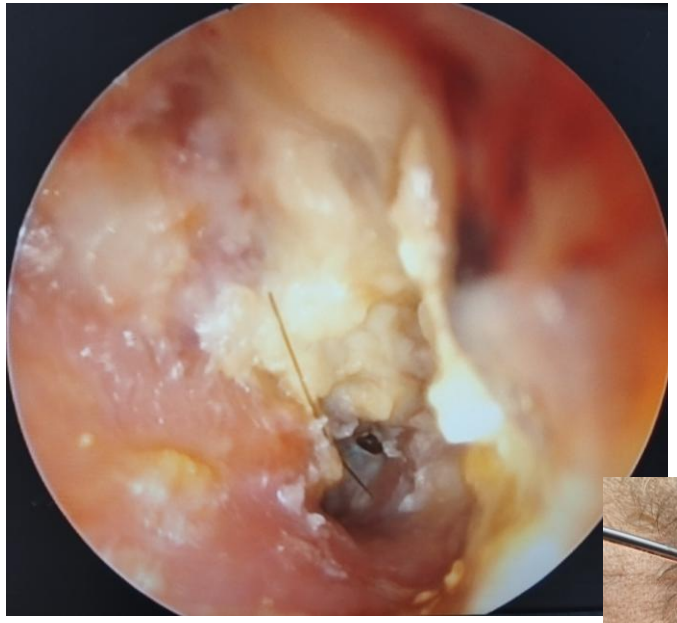
- **Traitement "instrumental" : systématique**, effectué en consultation
  - Il suffit parfois : aspirations répétées, bains d'oreille à l'eau oxygénée boratée…
  - **Supprimer les facteurs favorisants** en cas de récidive (humidité): **traitement de l'otite externe bactérienne ++**, voire exceptionnellement alésage du CAE sous AG, tympanoplastie...
- Place des antifongiques en traitement local :
  - AFSSAPS : Auricularum

    (nystatine pas toujours active sur les filaments… effet ASSECHANT de la forme en poudre ++)
  - Pévaryl lait ou lotion (inactif sur filaments)
  - Fungizone lotion dermique (pas si perforation : ampho B ototoxique)
  - Utilité des topiques locaux non démontrée +++



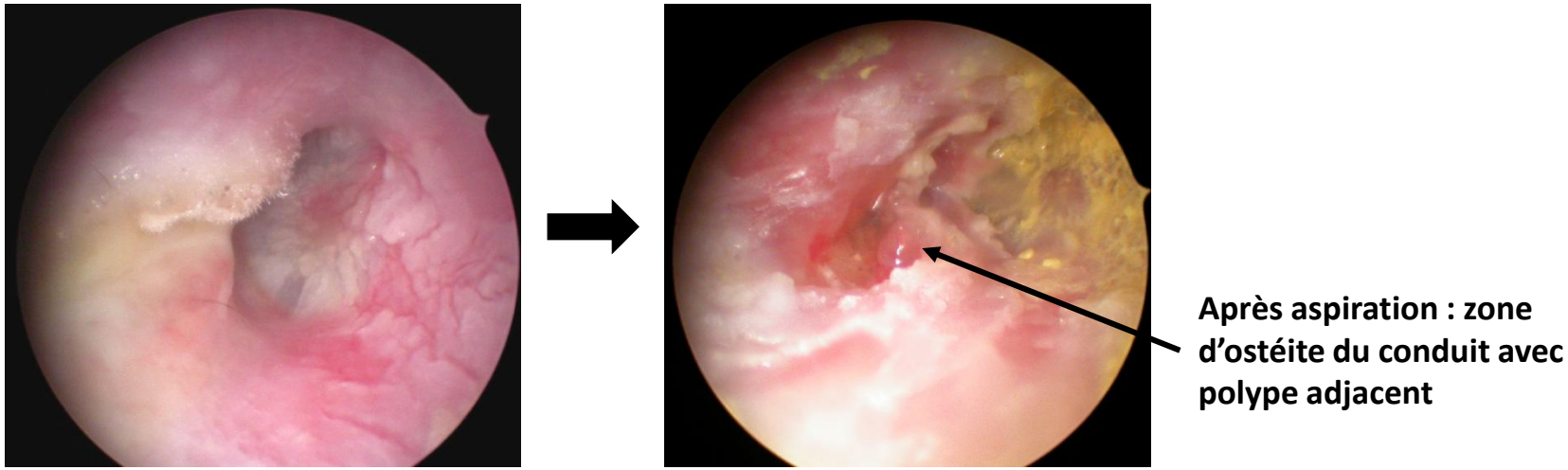
Perforation tympanique avec otorrhée

Patterson et al. Clin. Infect. Dis. 2016;63:433–442.



OTITE FONGIQUE INVASIVE

- Touchent les tissus mous < l'os sous-jacent (rocher)
- Jusqu'à 20% des otites malignes externes sont d'origine fongique (**Aspergillus**++)
- Terrain diabétique/immunodéprimé
- Cliniquement :
  - **Otalgie ++**
  - Sténose du conduit auditif externe et/ou otorrhée et/ou polypes du conduit
  - Apparition d'une perforation tympanique non présente initialement
  - Possible atteinte des nerfs crâniens : **paralysie faciale périphérique**



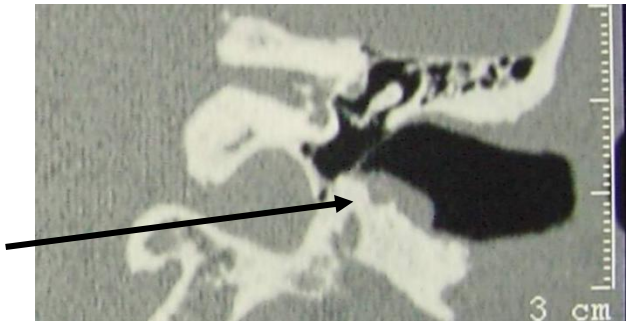
Après aspiration : zone d'ostéite du conduit avec polype adjacent

Le Clerc et al. Laryngoscope. 2014 Sep;124(9):2013-6. Mimram et al. soumis.

OTITE FONGIQUE INVASIVE

- Bilan initial :
  - **Fenêtre thérapeutique +++ tant que le pathogène n'est pas identifié**
  - Biopsies sous AL < AG avec anatomopathologie, mycologie, bactériologie
  - VS
  - TDM +/- IRM des rochers
  - Imagerie métabolique : TEP-TDM ou scintigraphie aux leucocytes marqués
- Traitement :
  - **Antifongiques par voie systémique** (durée > 6 mois ?) puis réévaluation
  - Chirurgie rarement nécessaire
  - Critères d'arrêt du traitement : disparition des douleurs, normalisation de l'otoscopie, de la VS et de l'imagerie métabolique (NB : normalisation beaucoup plus tardive des atteintes nerveuses, du scanner et de l'IRM)

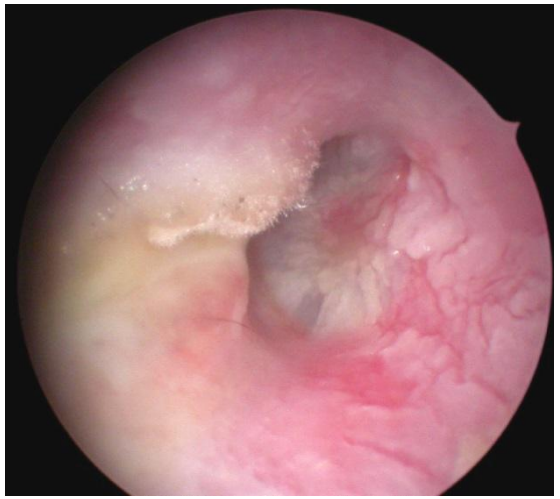
Lyse osseuse du plancher du conduit auditif

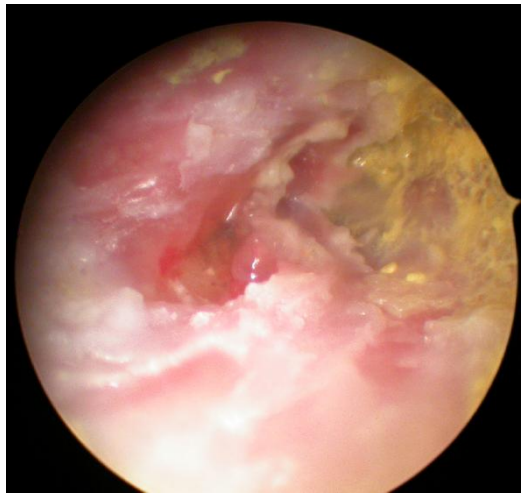


Marchionni et al. Clin. Microbiol. Infect. 2016 May;22(5):434-7
Patterson et al. Clin. Infect. Dis. 2016;63:433–442.

OTITE FONGIQUE INVASIVE : FORMES FRONTIÈRES

- Homme de 52 ans sans antécédent
- Fréquents voyages en Inde
- Otalgie chronique +++
- Traité depuis plus de 6 mois sans succès
- Aspect otoscopique :

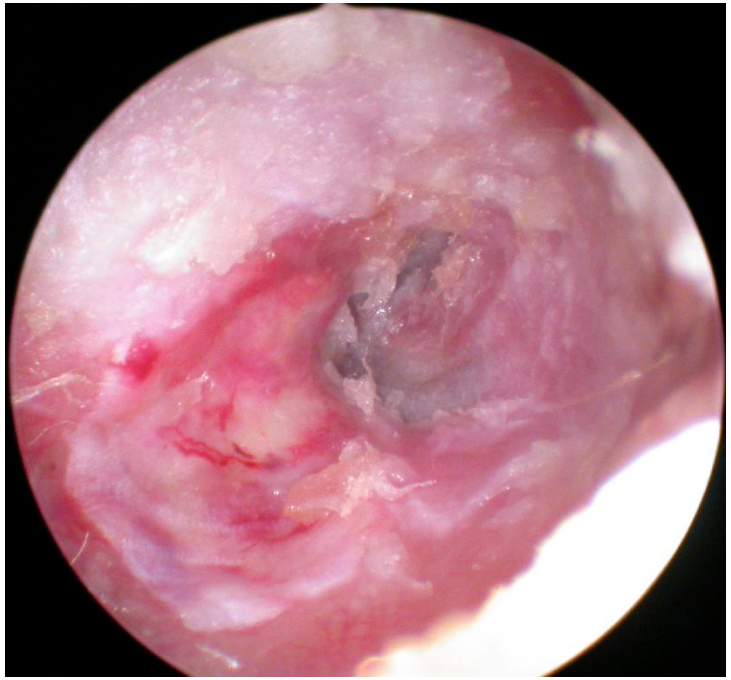




Quels examens complémentaires ?

3 cm

- Traitement antifongique local insuffisant au stade invasif (Fungizone)
- Curetage de l’ostéite avec couverture de l’os
- Traitement antifongique systémique? Voriconazole++



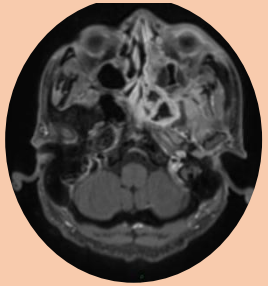
SINUSITES FONGIQUES

FUNGAL SINUSITIS

- **Non invasive:**
  - Fungal ball

  - Allergic Fungal Chronic Rhinosinusitis

- **Invasive:**
  - Acute



  - *Chronic and granulomatous invasive fungal sinusitis*

deShazo et al. N Engl J Med. 1997

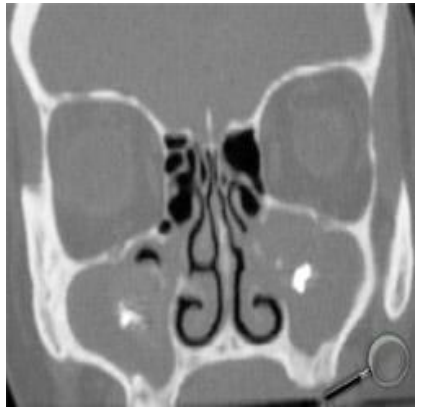
FUNGAL BALL

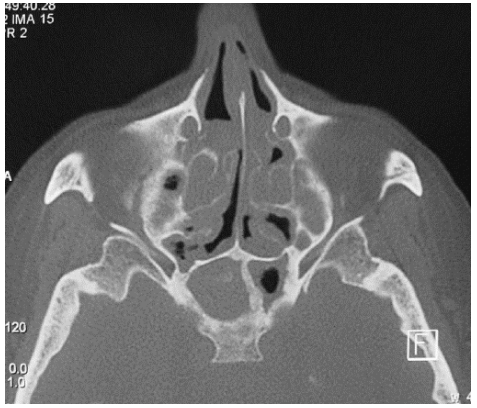
- **Frequent++**
- **Immunocompetent patients**
- Aspergillus sp. >> Fusarium sp. Or black fungi
- Maxillary sinus (+/- foreign body) > sphenoid > ethmoid > frontal
- **Main risk: bacterial superinfection** with potential complications
- Endoscopy:
  - Normal++
  - Purulent discharge in cases of bacterial superinfection
  - Rarely: fungal ball in the middle meatus

Dufour et al. Med Mycol. 2006
Dohin et al. Clin Otolaryngol. 2024

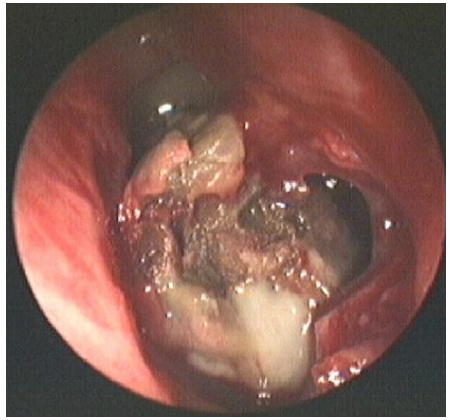
FUNGAL BALL

- Imaging:
  - CT :
    - Sinus filling
    - Spontaneaous hyperdensities « **calcifications** », sometimes foreign body
    - Osteitis
    - Rarely: « pseudotumoral » aspect
  - MRI: not mandatory… Hyposignal T2





- **Treatment:**
  - **Surgical removal of the fungal ball ++** : (endoscopy++), pathological samples (fungal ball and adjacent mucosa), mycology, bacteriology
  - No indication to antifungal systemic/topical treatment



Dufour et al. Med Mycol. 2006
Patterson et al. Clin. Infect. Dis. 2016


) RFMT
13.1cm
Aug 25 2
Mag = 1
AVERAGE

AFRS

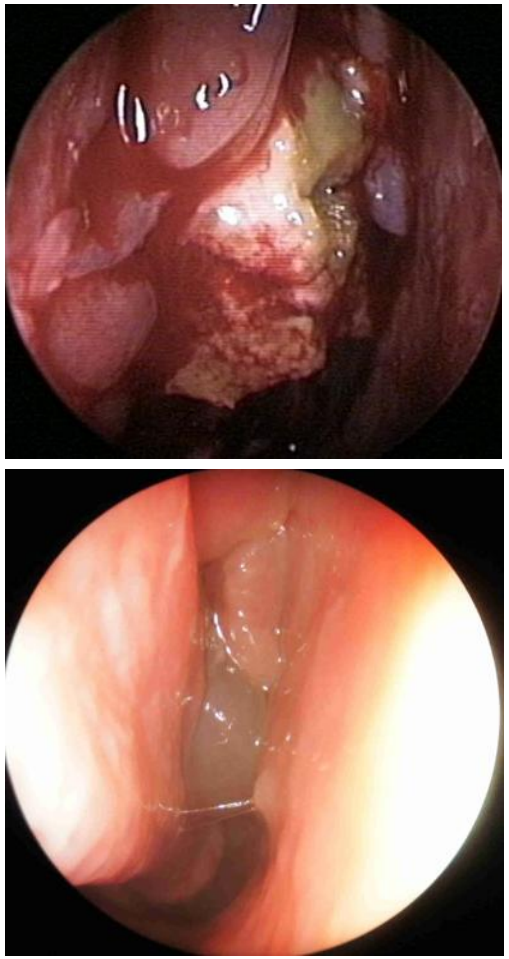
- IgE-mediated type I hypersensitivity to fungal allergens (cf Allergic Bronchopulmonary Aspergillosis): atopic patients
- Type 2 inflammation
- AFRS and other CRSwNP: distinct molecular profiles
- More frequent in warm climates (high fungal load)
- Aspergillus flavus (India/Middle East) > A fumigatus (Europe)

→ NON-INVASIVE fungal rhinosinusitis immunocompetent patients

Schubert et al. J Allergy Clin Immunol. 1998
Tyler et al. Otolaryngol Head Neck Surg. 2018
Gan et al. Int. Forum Allergy Rhinol. 2014
Chakrabarti et al. J Fungi (Basel). 2016

AFRS: CLINICAL PRESENTATION

- **Severe diffuse chronic rhinosinusitis**
  - Nasal obstruction, anosmia…
  - Nasal polyps +/- mucin
  - Recurrence++ after OCS and/or surgery



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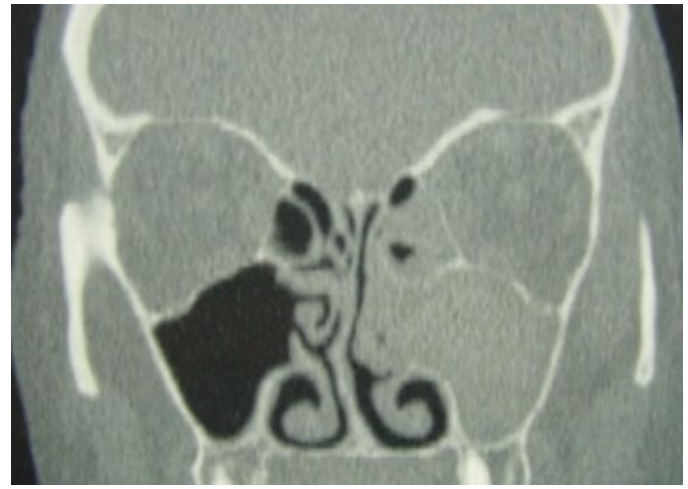
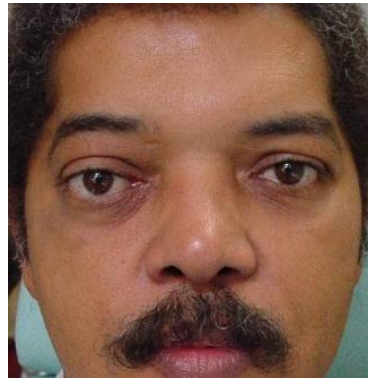


- **Localized/unilateral CRS**

- **Pseudo-tumoral presentation**: progressive proptosis…



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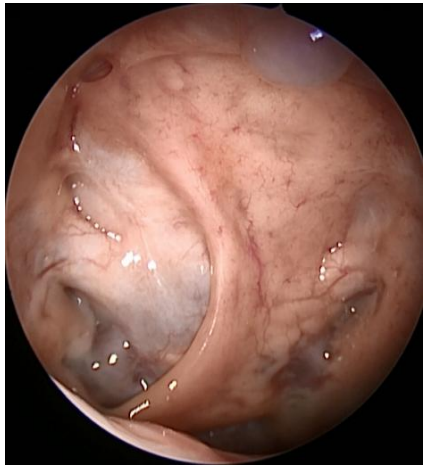

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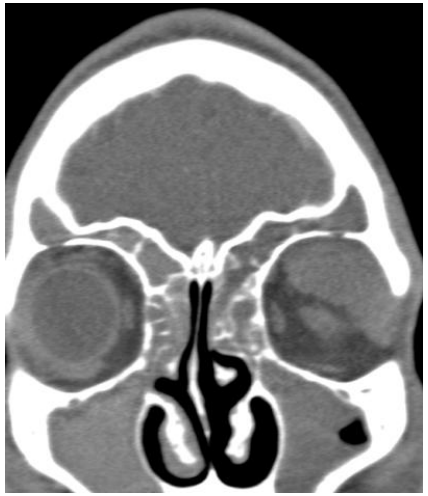

- **Acute presentation**: in case of bone erosion due to mucin accumulation (sphenoid sinus: loss of vision…)

AFRS: WORK-UP

- Elevated levels of peripheral eosinophilia + total and fungal-specific (A Flavus/Fumigatus++) IgE

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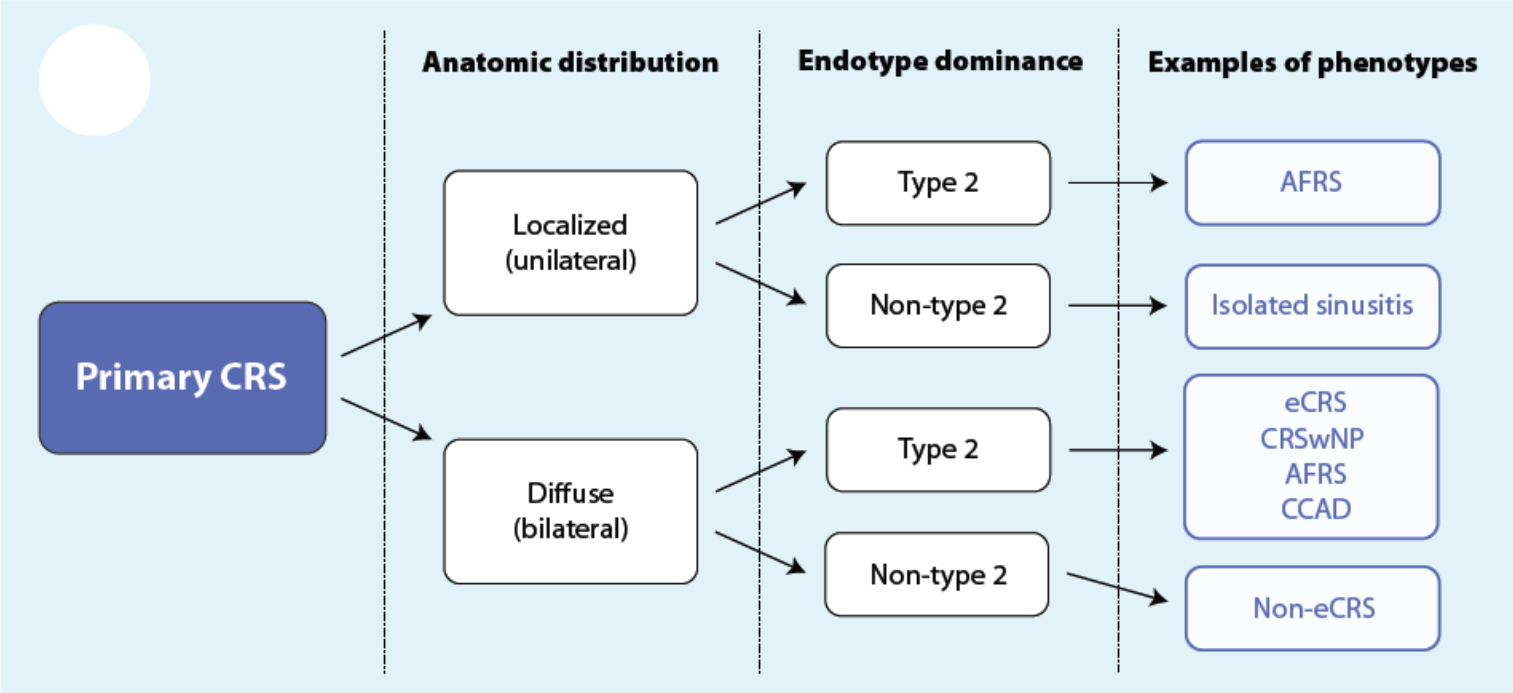
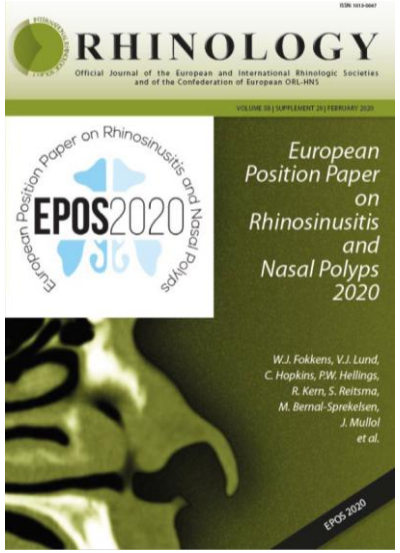
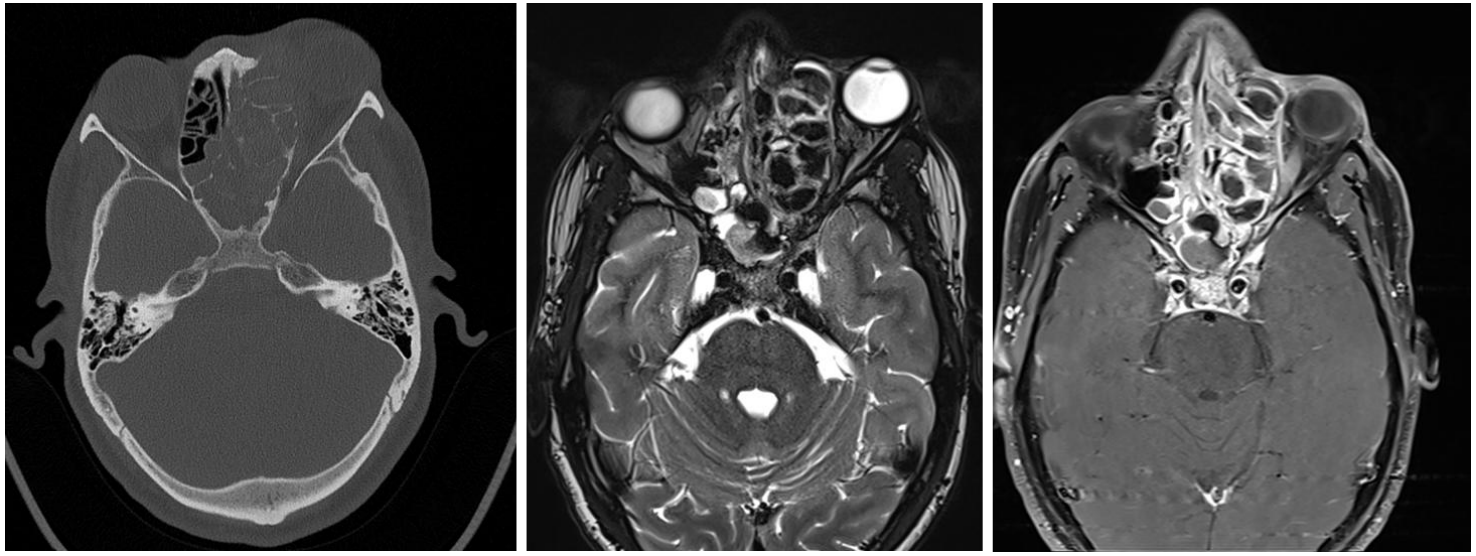




AFRS: WORK-UP

- Elevated levels of peripheral eosinophilia + total and fungal-specific (A Flavus/Fumigatus++) IgE

- IMAGING:
  - CT: sinus filling +/- hyperdense +/- bony remodeling and erosion
  - MRI: hyposignal on T2, no enhancement on T1+ gadolinium



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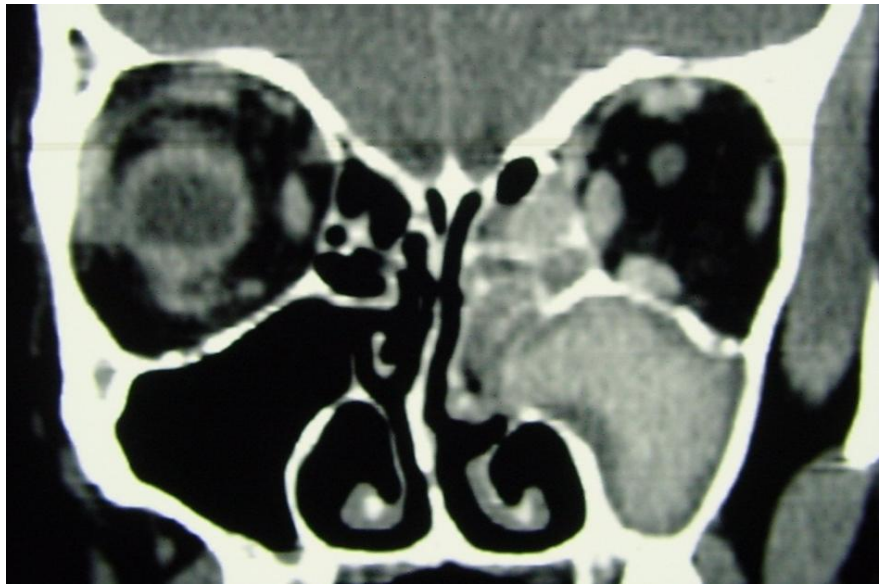
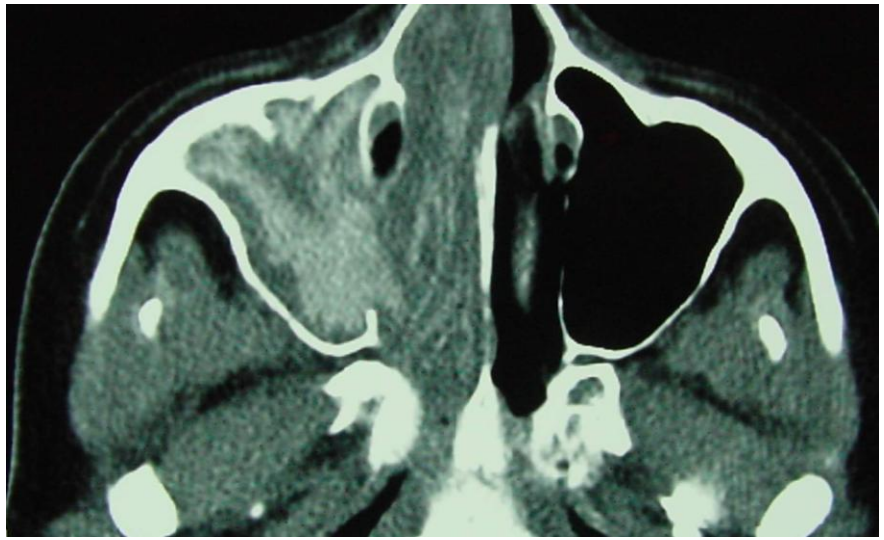
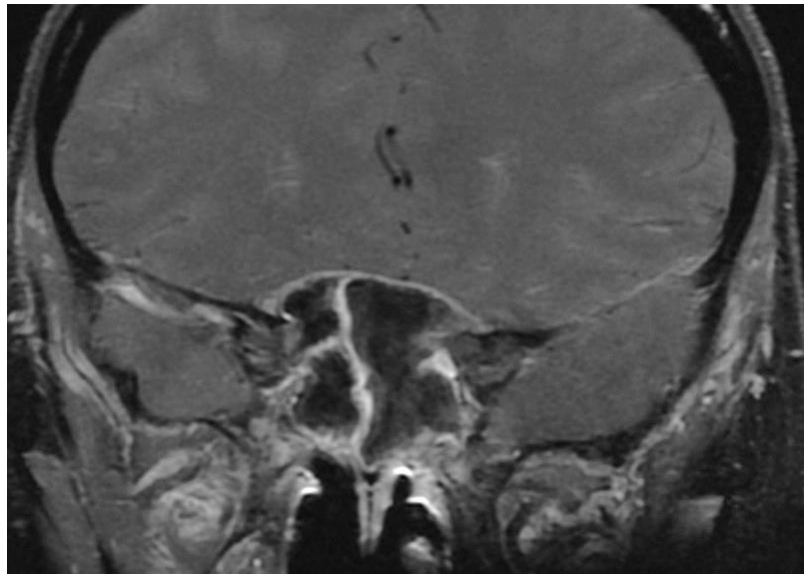
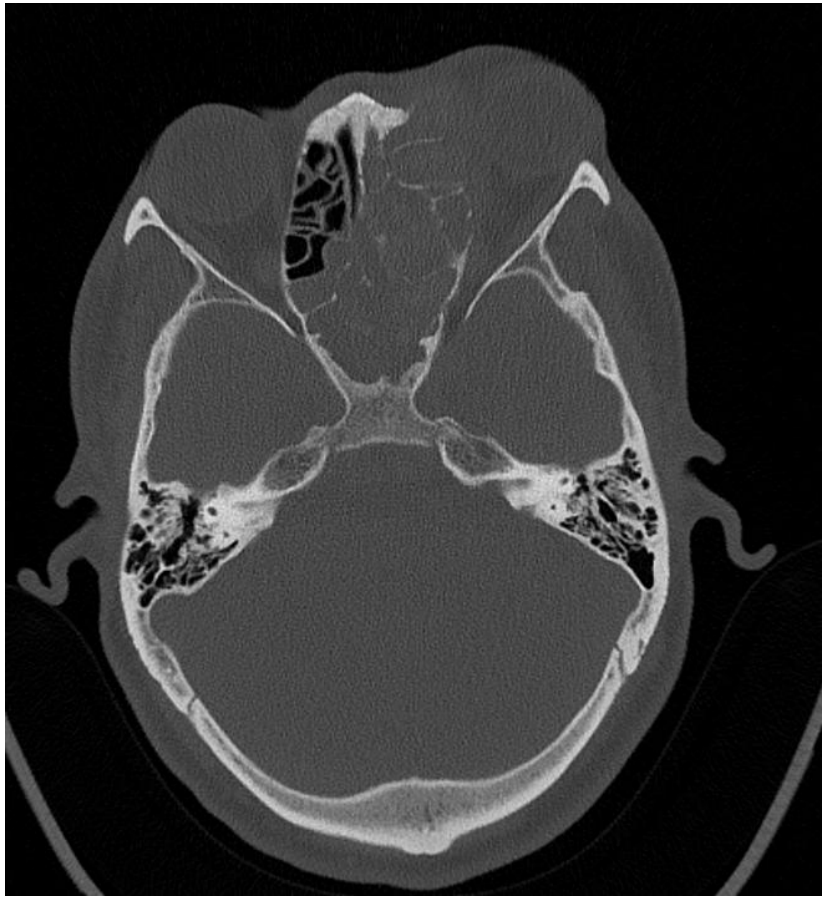
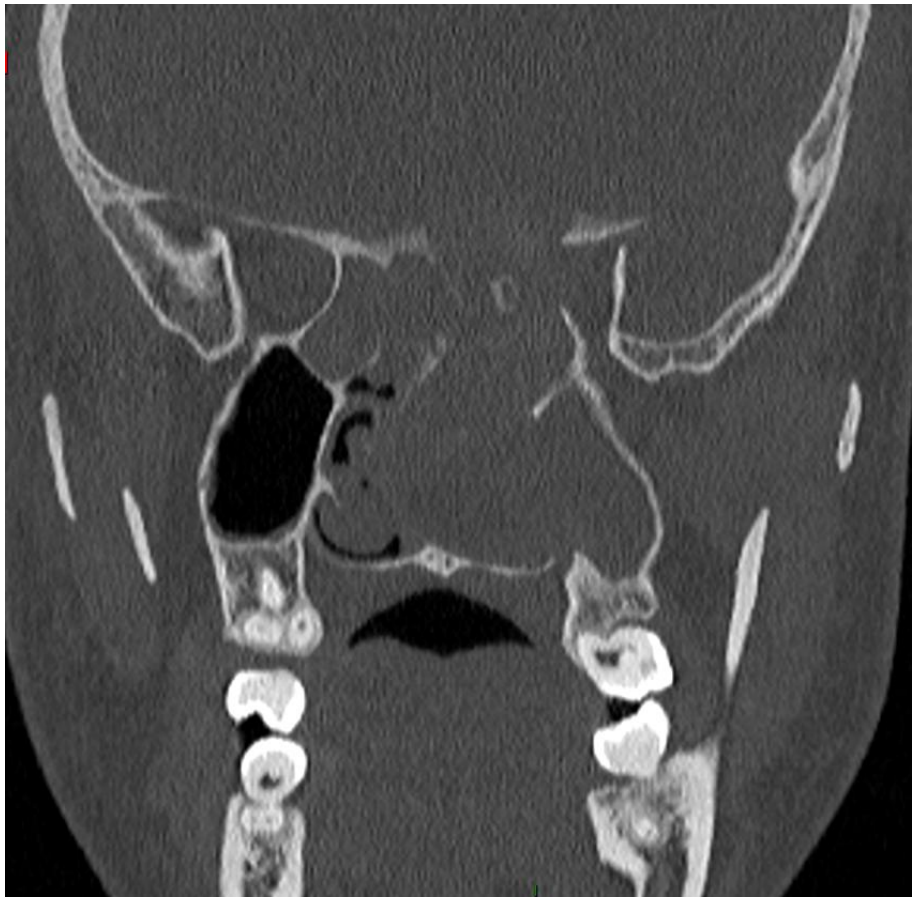






M. A, 32 ans, exophtalmie gauche progressive…





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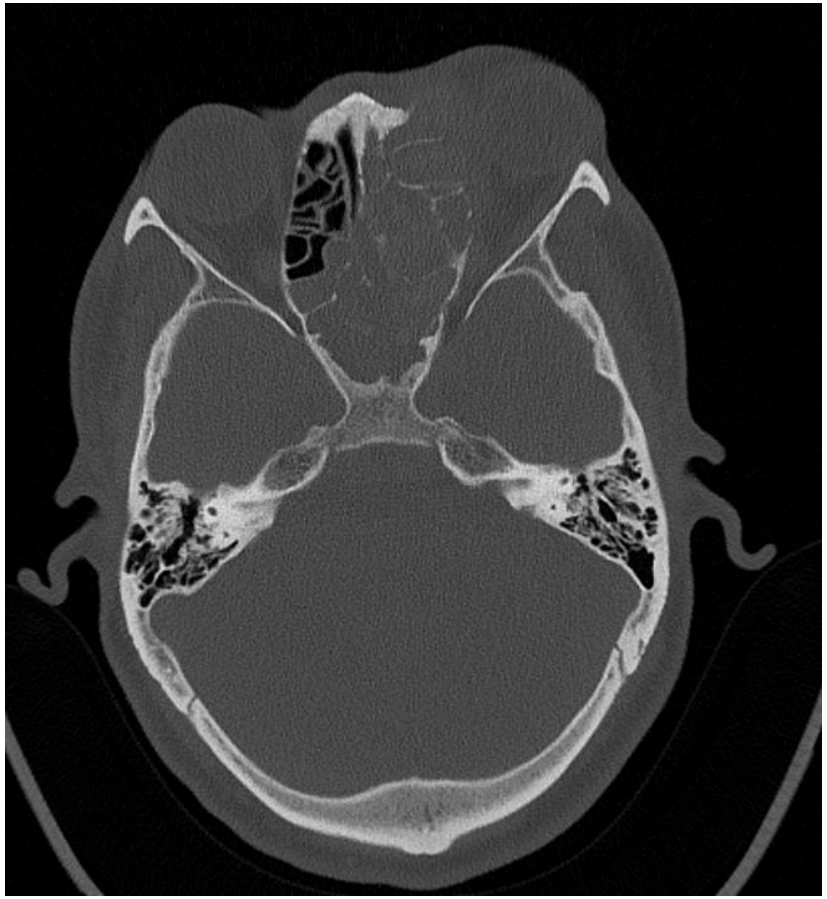

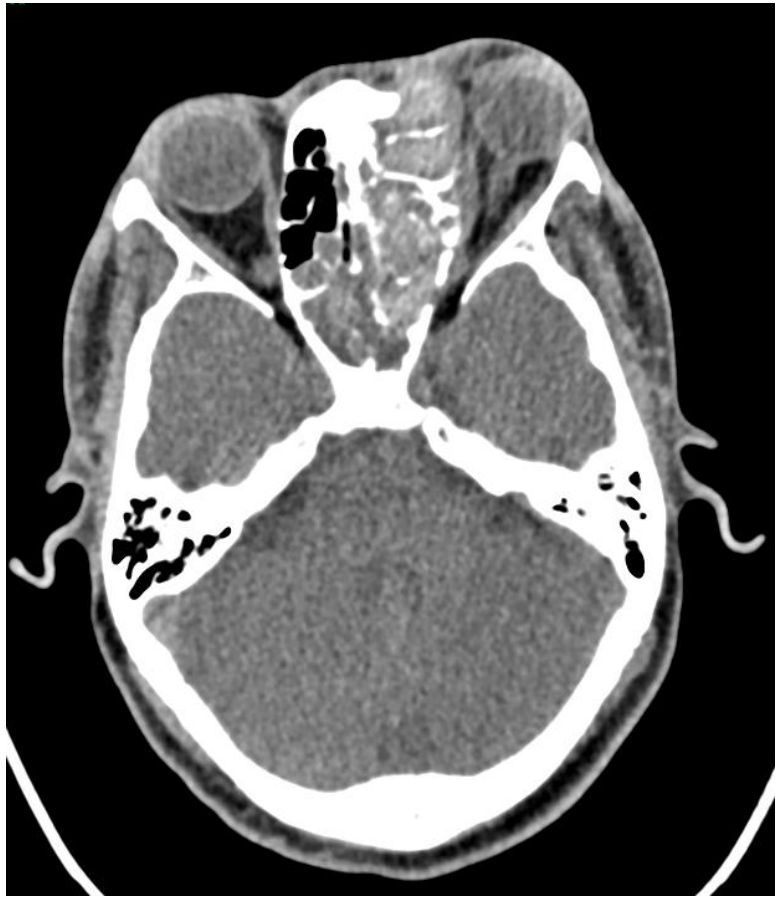

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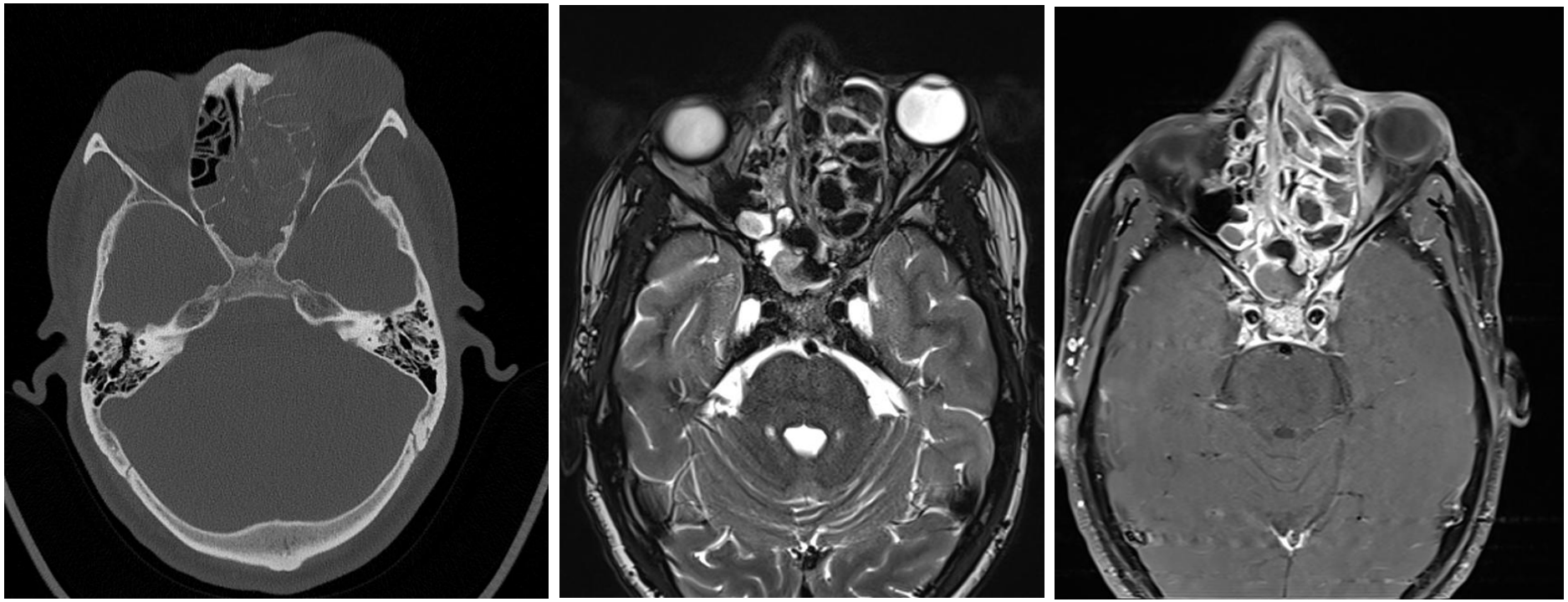
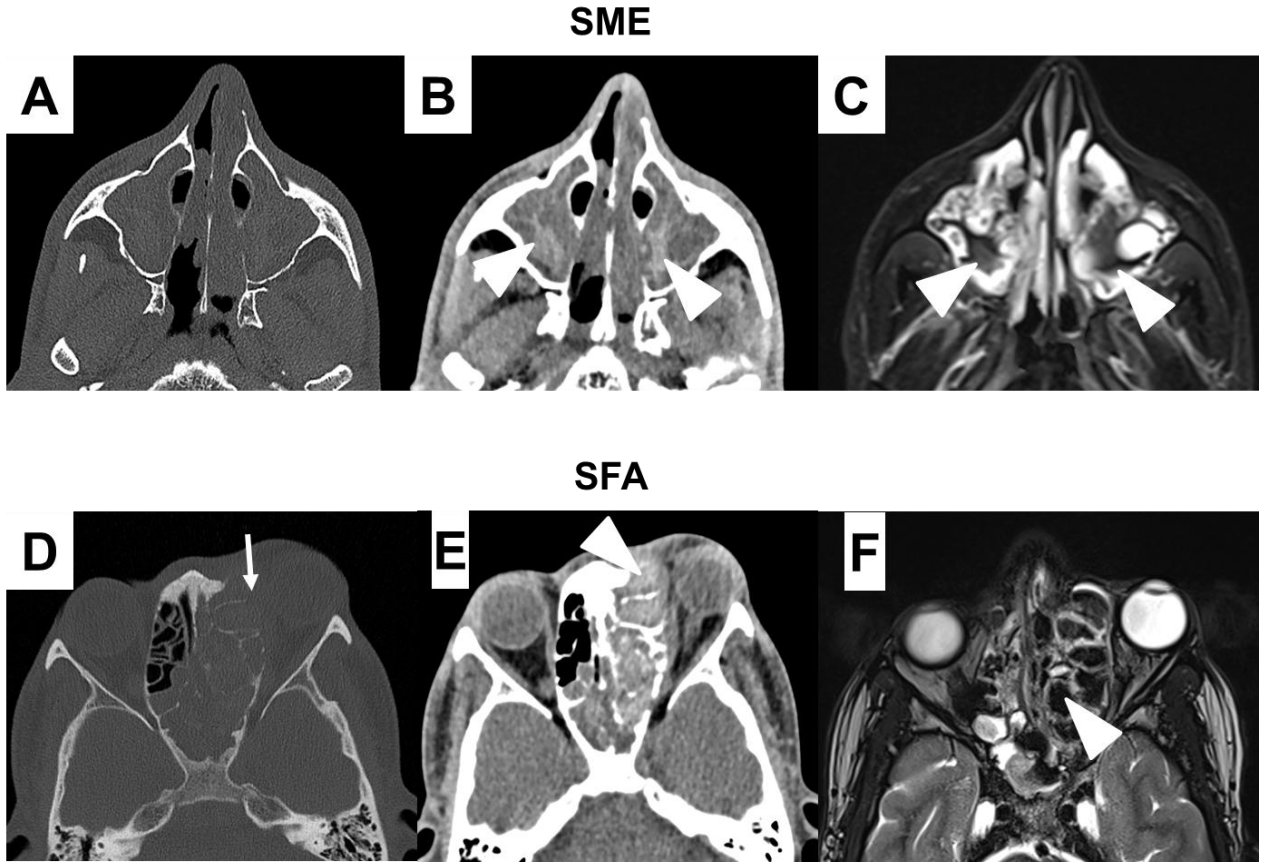


AFRS: DIFFERENTIAL DIAGNOSIS



The Laryngoscope
Lippincott Williams & Wilkins, Inc., Philadelphia

CANDIDATE'S THESIS

Eosinophilic Mucin Rhinosinusitis: A Distinct Clinicopathological Entity

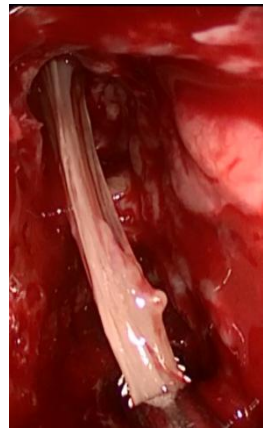
Dubois et al. Eur Ann Otorhinolaryngol Head Neck Dis. 2023

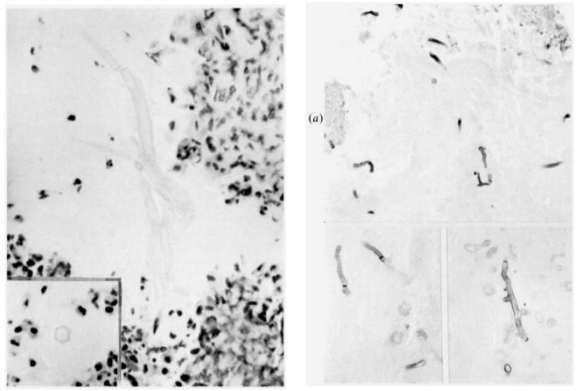
AFRS: TREATMENT

- General therapeutic strategy:
  - Surgical removal of all the mucin++
  - Oral corticosteroids
  - Topical steroids
  - 10 to 100% recurrence!

Typical aspect of the mucin:

Eosinophilic infiltrate + Charcot-Leyden cristals + Scattered fungal hyphae
Inflammation of adjacent mucosa with eosinophilic infiltrate but NO fungal invasion

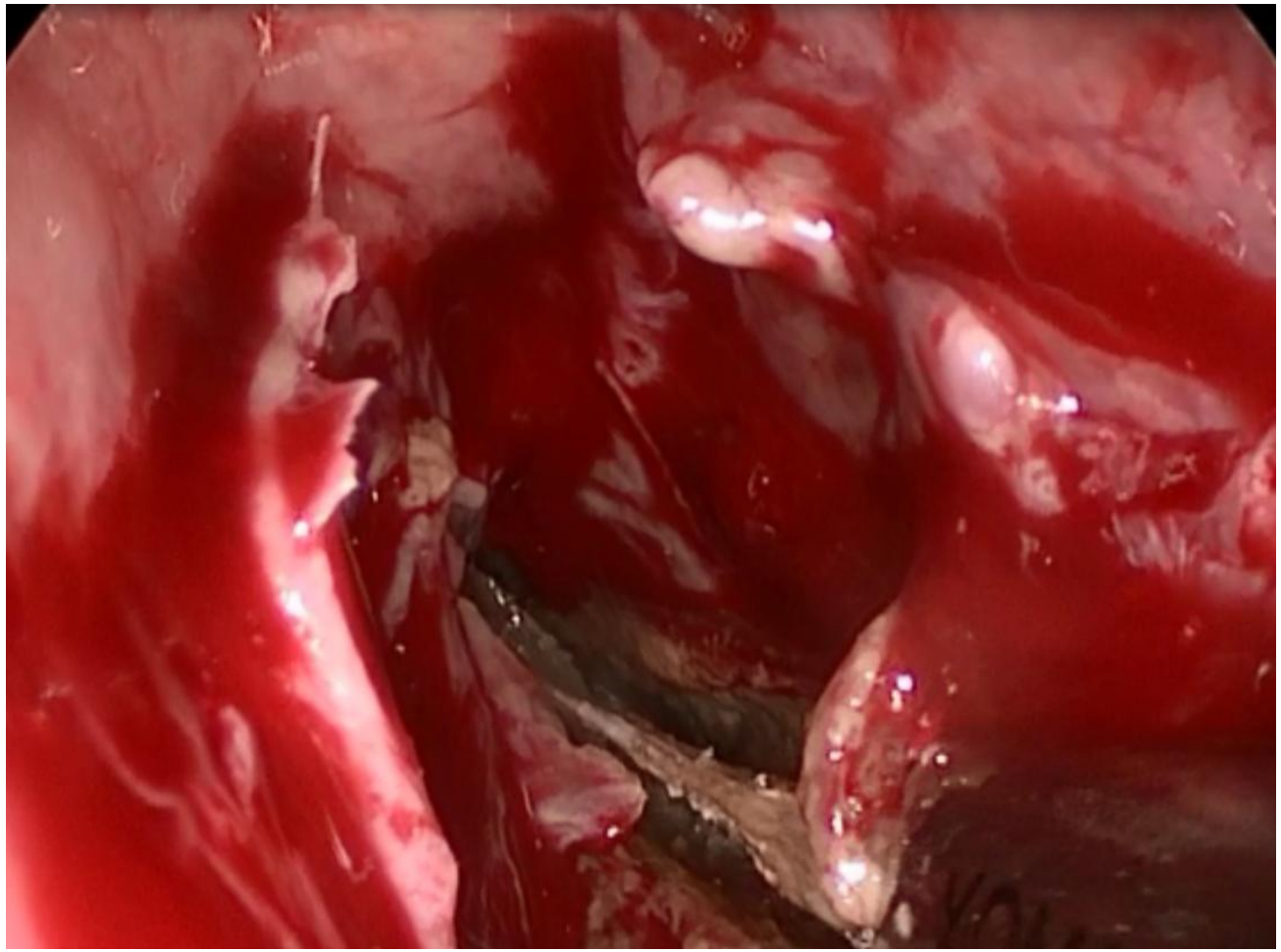




- Systemic antifungal therapy (voriconazole) : probably not necessary… or only in case of recurrent AFRS?

- *Allergen immunotherapy? Topical antifungal therapy?*

Katzenstein et al. Am J Surg Pathol. 1983
Lafont et al., Revue des Maladies Respiratoires.2017
Patterson et al. Clin. Infect. Dis. 2016
Bent III JP, Kuhn A. Oto-laryngol Head Neck Surg. 1994.
deShazo RD, Swain RE. J of Allergy & Clinical Immunology 1995



AFRS: BENT & KUHN DIAGNOSTIC CRITERIA

Diagnosis of allergic fungal sinusitis

- Major criteria:
  - Nasal polyposis
  - Fungi on staining
  - Eosinophilic mucin
  - No fungal invasion into sinus tissue
  - Type I hypersensitivity to fungi
  - Characteristic CT findings

- Minor criteria
  - Asthma
  - Bone erosion
  - Charcot Leyden Crystals
  - Unilateral disease
  - Peripheral eosinophilia
  - Positive fungal culture

- deShazo criteria:
  - Eosinophilic mucin
  - Characteristics CT/MR findings
  - Fungi: positive staining OR culture
  - No fungal invasion into sinus tissue
  - Absence of immunodeficiency or diabetes

Bent III JP, Kuhn A. Oto-laryngol Head Neck Surg. 1994;111:580—8.
deShazo RD, Swain RE. J of Allergy & Clinical Immunology 1995;96:24-35.

Mme M. , 41 ans, sinusite invasive à fusarium ?

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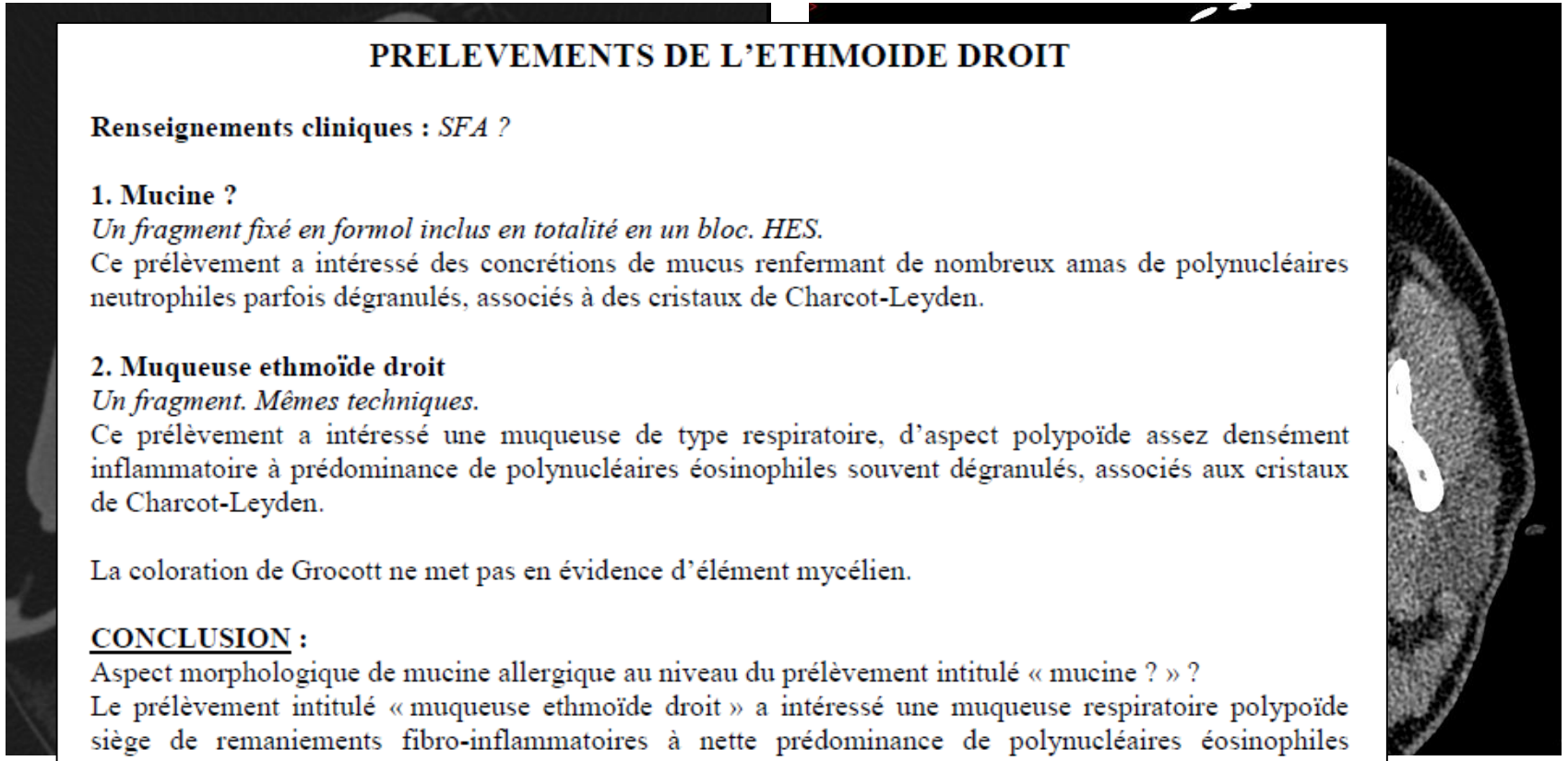


PRELEVEMENTS DE L'ETHMOIDE DROIT

Renseignements cliniques : *SFA ?*

1. Mucine ?

Un fragment fixé en formol inclus en totalité en un bloc. HES.

Ce prélèvement a intéressé des concrétions de mucus renfermant de nombreux amas de polynucléaires neutrophiles parfois dégranulés, associés à des cristaux de Charcot-Leyden.

2. Muqueuse ethmoïde droit

Un fragment. Mêmes techniques.

Ce prélèvement a intéressé une muqueuse de type respiratoire, d'aspect polypoïde assez densément inflammatoire à prédominance de polynucléaires éosinophiles souvent dégranulés, associés aux cristaux de Charcot-Leyden.

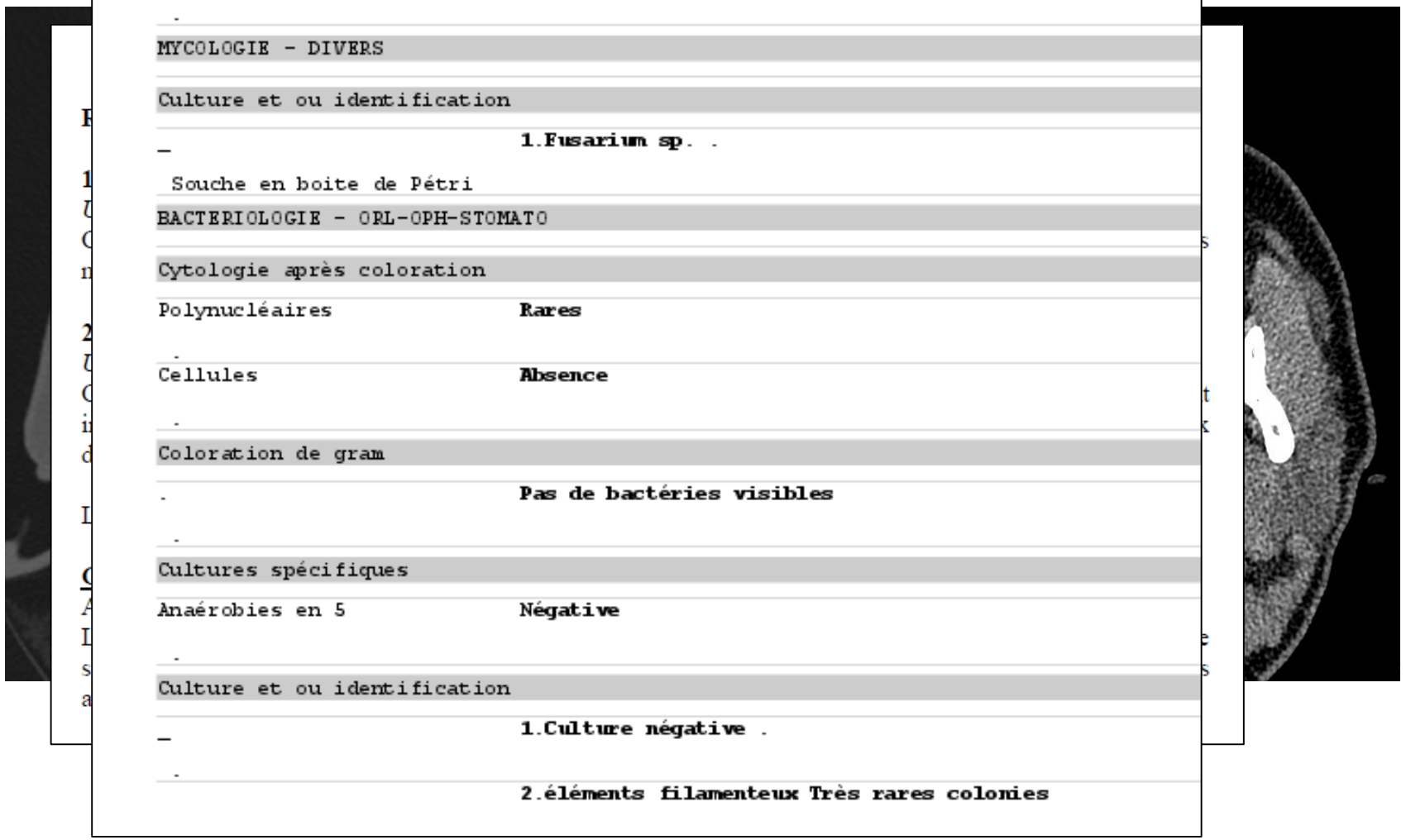
La coloration de Grocott ne met pas en évidence d'élément mycélien.

CONCLUSION :

Aspect morphologique de mucine allergique au niveau du prélèvement intitulé « mucine ? » ?

Le prélèvement intitulé « muqueuse ethmoïde droit » a intéressé une muqueuse respiratoire polypoïde siège de remaniements fibro-inflammatoires à nette prédominance de polynucléaires éosinophiles associés aux cristaux de Charcot-Leyden.

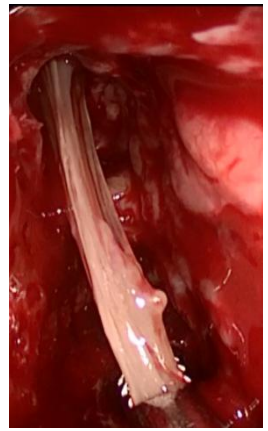
Mme M. , 41 ans, sinusite invasive à fusarium ?



Type de lésion	**Non précisé**
MYCOLOGIE - DIVERS	
Culture et ou identification	
_	**1.Fusarium sp. .**
Souche en boite de Pétri	
BACTERIOLOGIE - ORL-OPH-STOMATO	
Cytologie après coloration	
Polynucléaires	**Rares**
Cellules	**Absence**
Coloration de gram	
.	**Pas de bactéries visibles**
Cultures spécifiques	
Anaérobies en 5	**Négative**
Culture et ou identification	
_	**1.Culture négative .**
	2.éléments filamenteux Très rares colonies

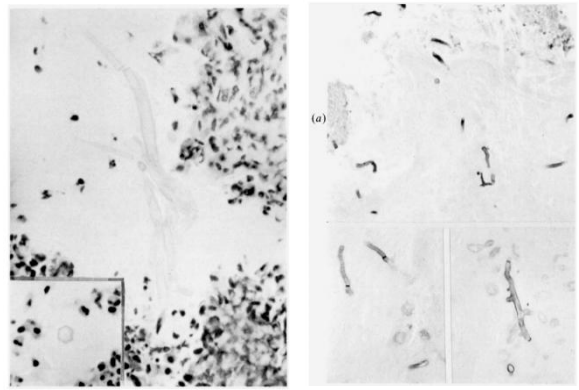
AFRS: TREATMENT

- General therapeutic strategy:
  - Surgical removal of all the mucin++
  - Oral corticosteroids
  - Topical steroids
  - 10 to 100% recurrence!

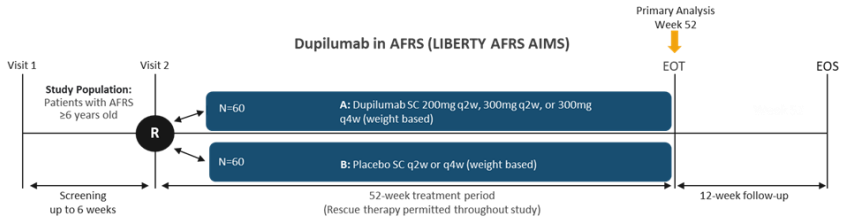


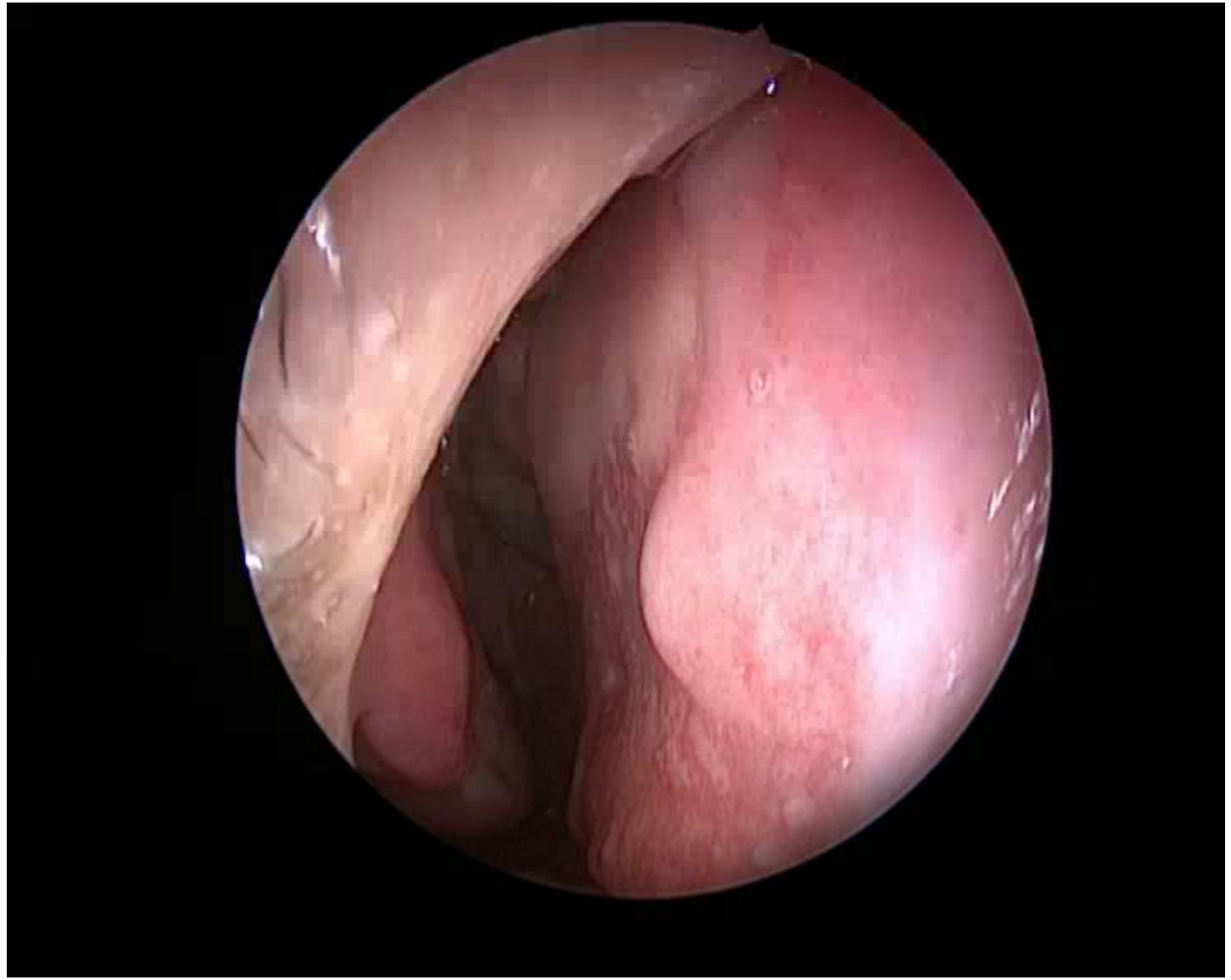
Typical aspect of the mucin:

Eosinophilic infiltrate + Charcot-Leyden cristals + Scattered fungal hyphae
Inflammation of adjacent mucosa with eosinophilic infiltrate but NO fungal invasion



- Systemic antifungal therapy (voriconazole) : probably not necessary… or only in case of recurrent AFRS?
- *Allergen immunotherapy? Topical antifungal therapy?*
- BIOLOGICS? Phase 3 trial of Dupilumab in AFRS





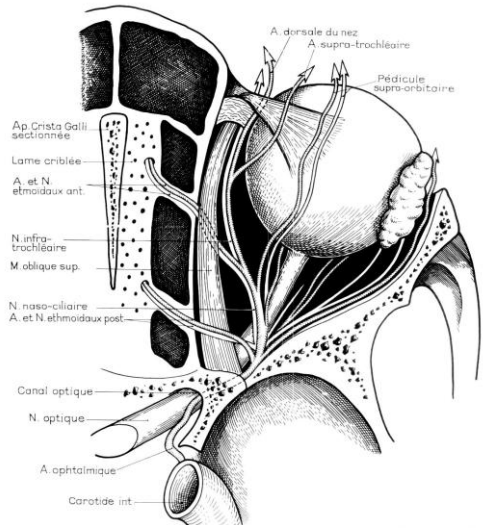
INVASIVE FUNGAL RHINOSINUSITIS

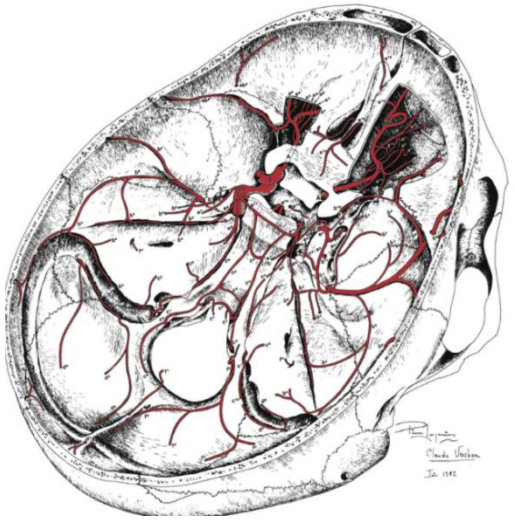
- **Invasive aspergillosis (aspergillus fumigatus++) > mucormycosis**
  rarely: Fusarium, Scedosporium, Alternaria…

- **Rising incidence**

- **OPPORTUNISTIC INFECTION => Underlying condition: diabetes mellitus (mucormycosis) and immunodeficiency**++ hemopathy (acute leukemia and invasive aspergillosis++), chemotherapy, immunosuppressive treatments (transplant patients), stem cell transplants, burns….

INVASION OF BLOOD VESSELS = INFECTION SPREADING THROUGH NATURAL FISSURES/FORAMINA: RHINO-CEREBRO-ORBITAL FORMS

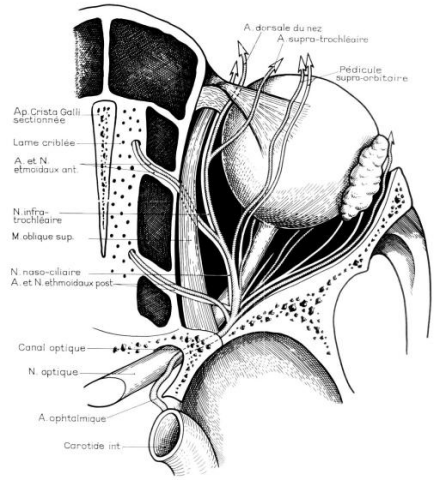




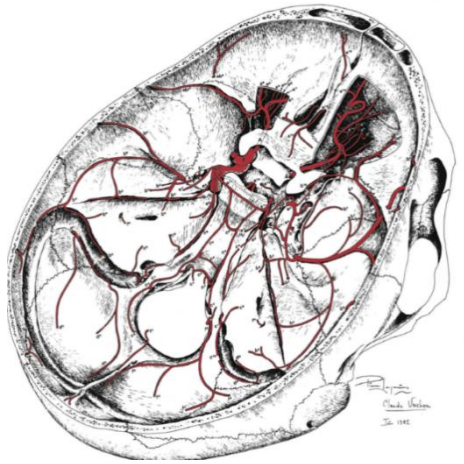
Lortholary et al. Clin Microbiol Infect.
Binder et al. Clin Microbiol Infect.

PRESENTING SIGNS

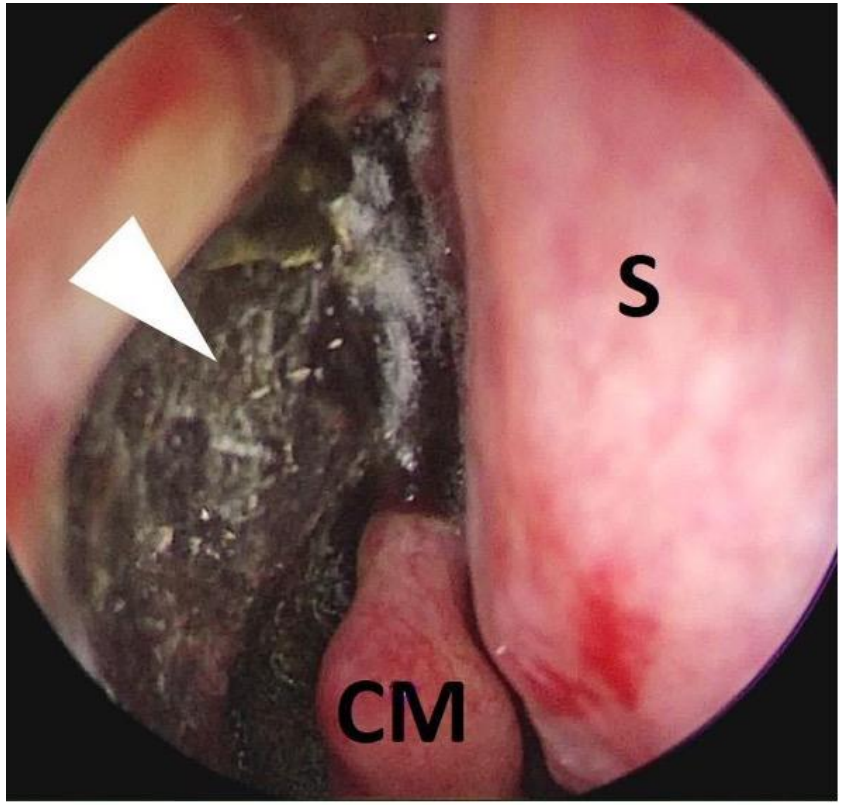
- Rhinological signs:
  - NON SPECIFIC symptoms at early stage: **pain**++, nasal congestion/discharge
  - Nasal endoscopy: +/- inflammation, **necrotic aspect of the mucosa** (mucormycosis++)



- Extranasal signs:
  - **Extension through natural fissures/foramina to adjacent regions: angiotropism of *Mucorales*++**
    - **Orbital invasion**: chemosis, diplopia, proptosis, loss of vision
    - Skin necrosis (cheek, eyelid, nose), hard palate
    - Facial numbness
    - Neurological signs in case of intracranial extension
    - ICA invasion: risk of septic embolism/stroke



Patterson et al. Clin. Infect. Dis. 2016
Lanternier et al. Clin Infect Dis 2012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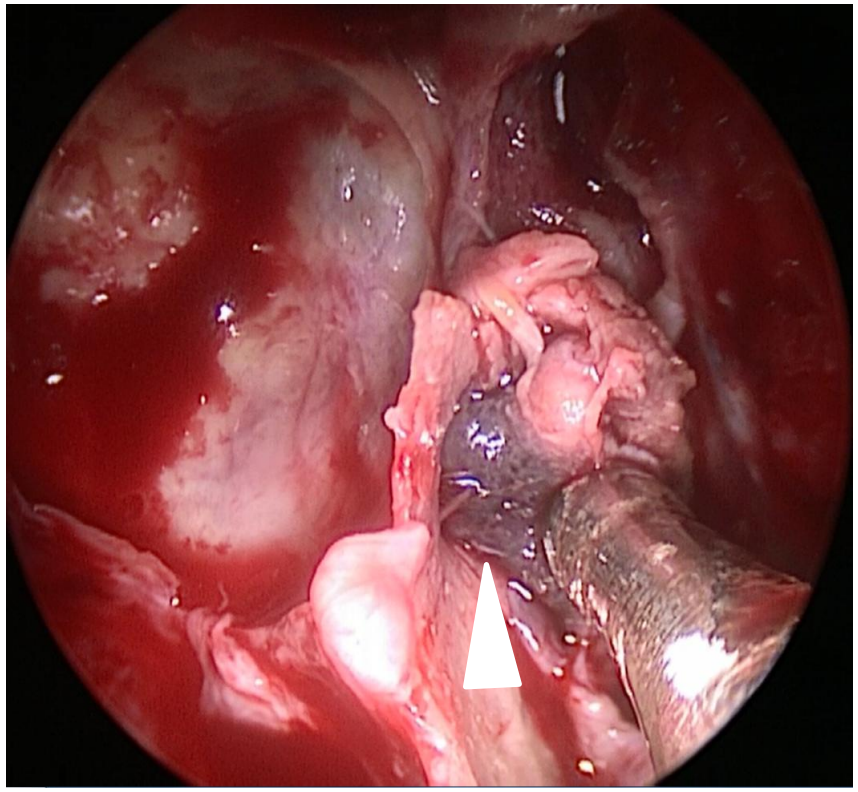
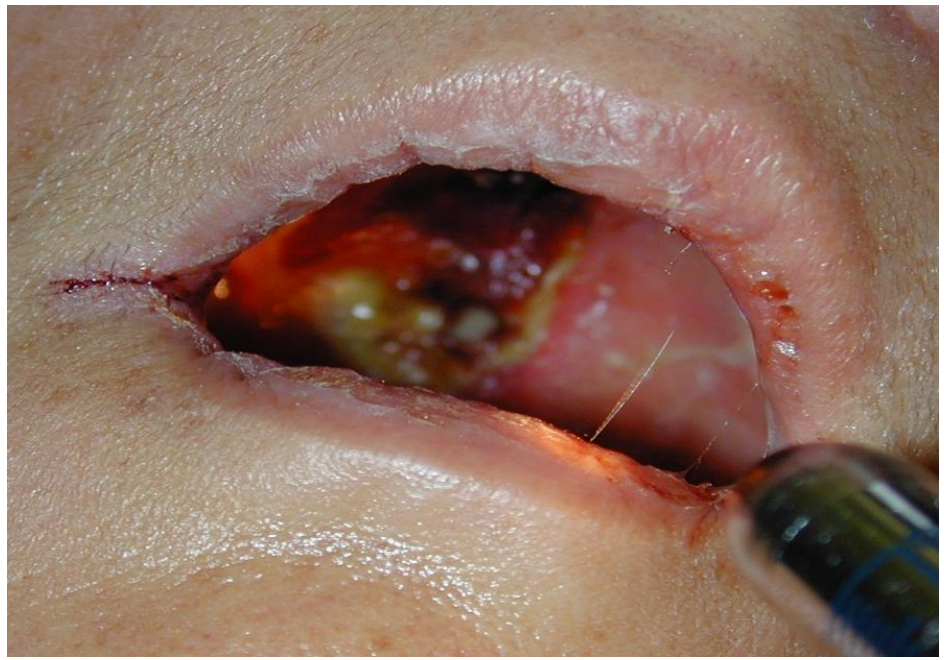




THE OCCURRENCE OF ANY SINONASAL SYMPTOM IN AN IMMUNOSUPPRESSED PATIENT WARRANTS AN URGENT ENT EXAMINATION

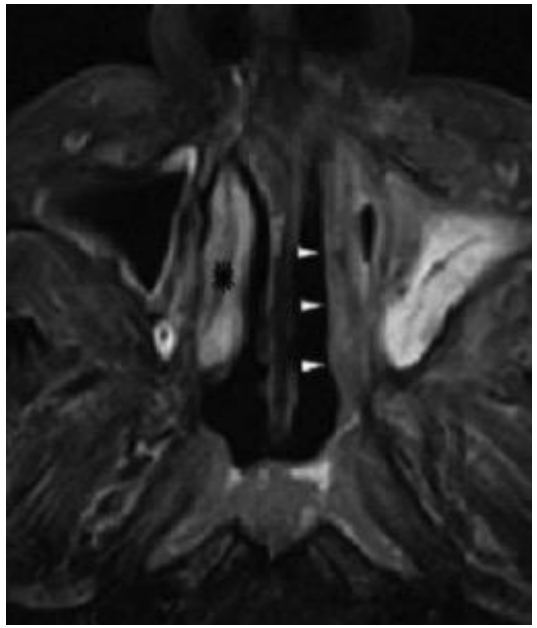
IMAGING WORK-UP

- CT :
  - Initially: non specific signs (mucosal thickening/sinus filling)
  - Bone lysis at more advanced stages

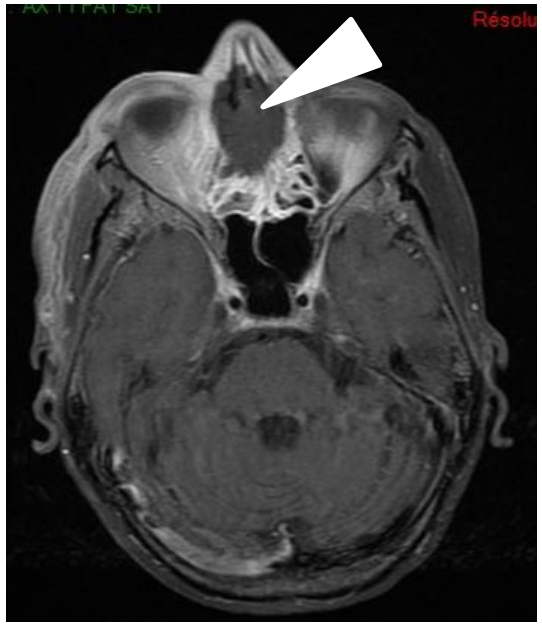
Raz et al. Neuroimaging Clin N Am. 2015

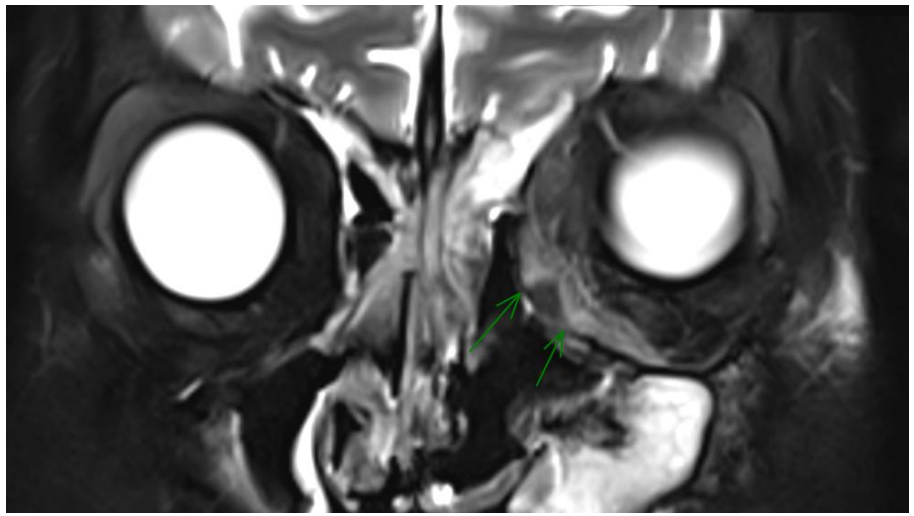
IMAGING WORK-UP

- MRI :
  - Soft tissues assessment: *black turbinate sign* < **ORBITAL AND INTRACRANIAL EXTENSION**
  - Angioinvasion for *Mucorales*
  - **Useful for follow-up**

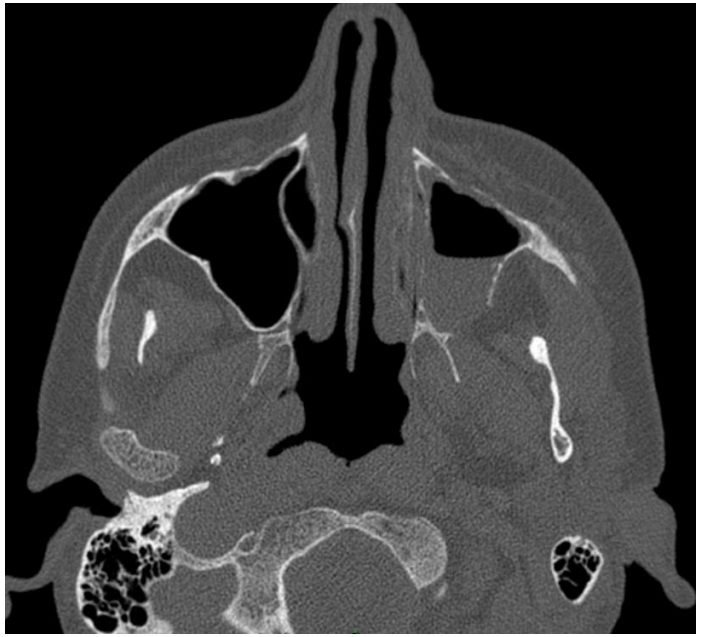


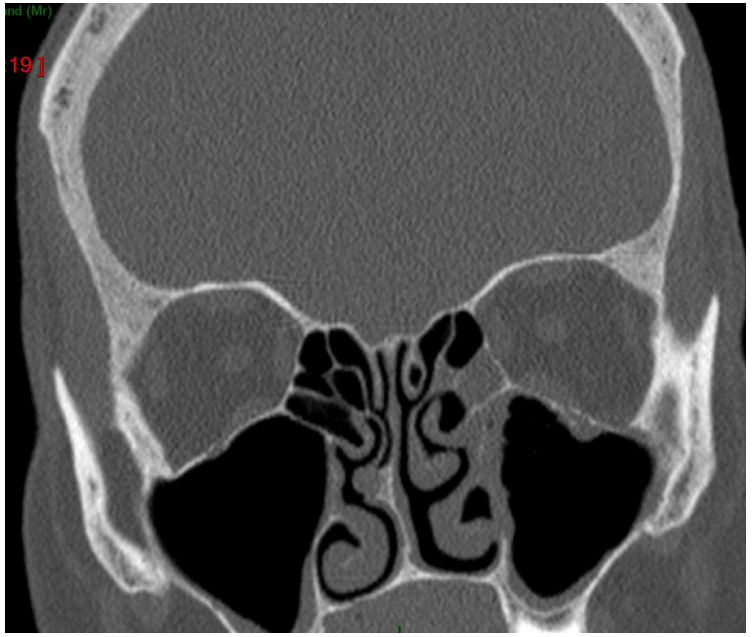
« Black turbinate » sign





Raz et al. Neuroimaging Clin N Am. 2015

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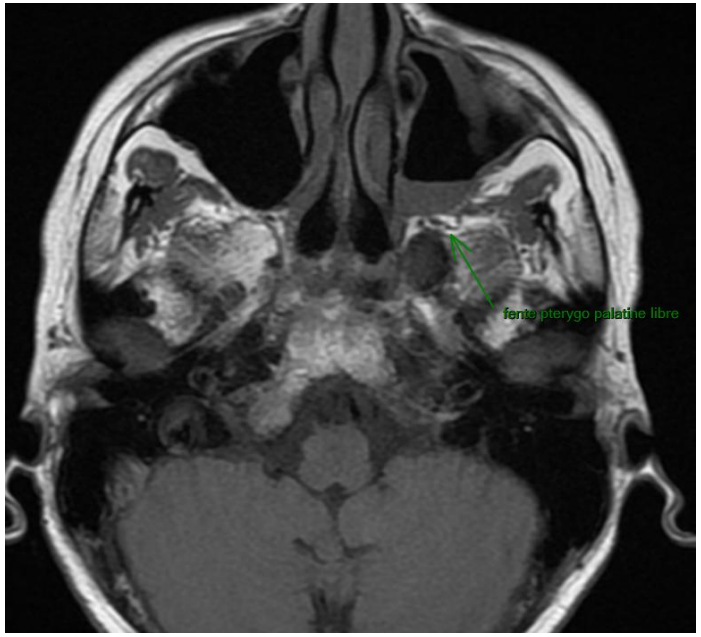
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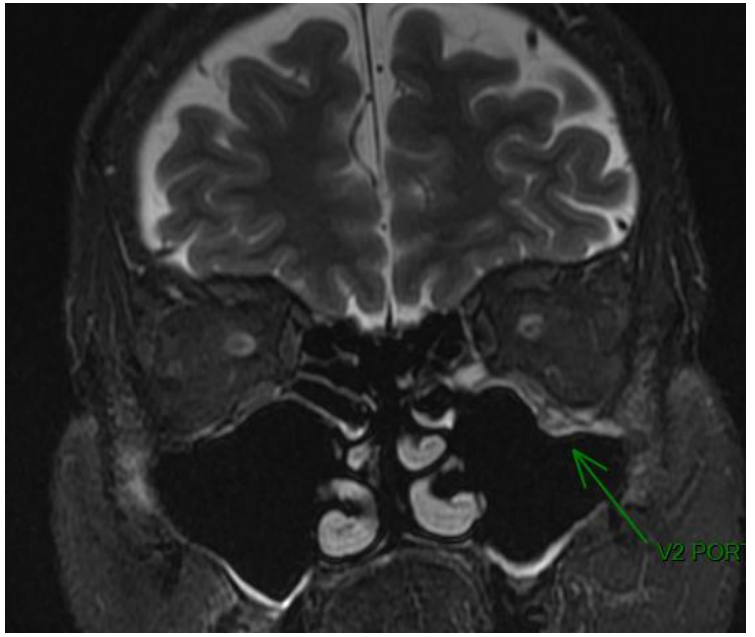

V2 POR

WORK-UP

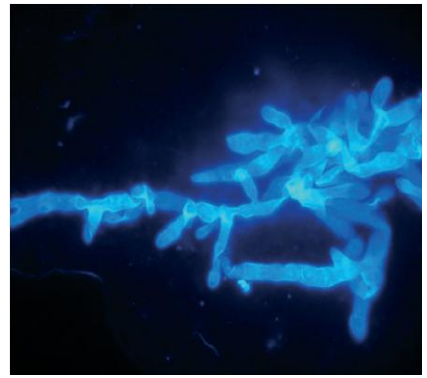
URGENT BIOPSY FOR MYCOLOGICAL AND PATHOLOGICAL EXAMINATION

- Mycology:
  - Direct microscopic examination++
  - Culture: difficult… identification of fungal species and antifungigram++

- **Histopathologic examination :**
  - Mucormycosis: non-septated or minimally septated broad, ribbon-like hyphae
  - Angioinvasion for *Mucorales:* necrosis and septic thrombi

- PCR on tissue: frozen specimen

- General work-up: PCR Aspergillus and Mucorale (plasma), Galactomannan antigen, chest CT, assessment of the underlying condition (diabetes mellitus…)



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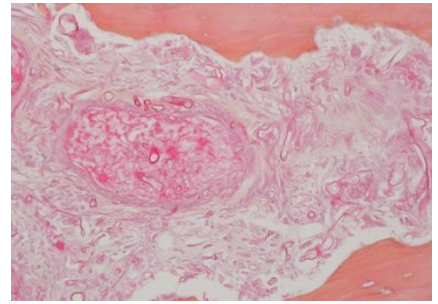
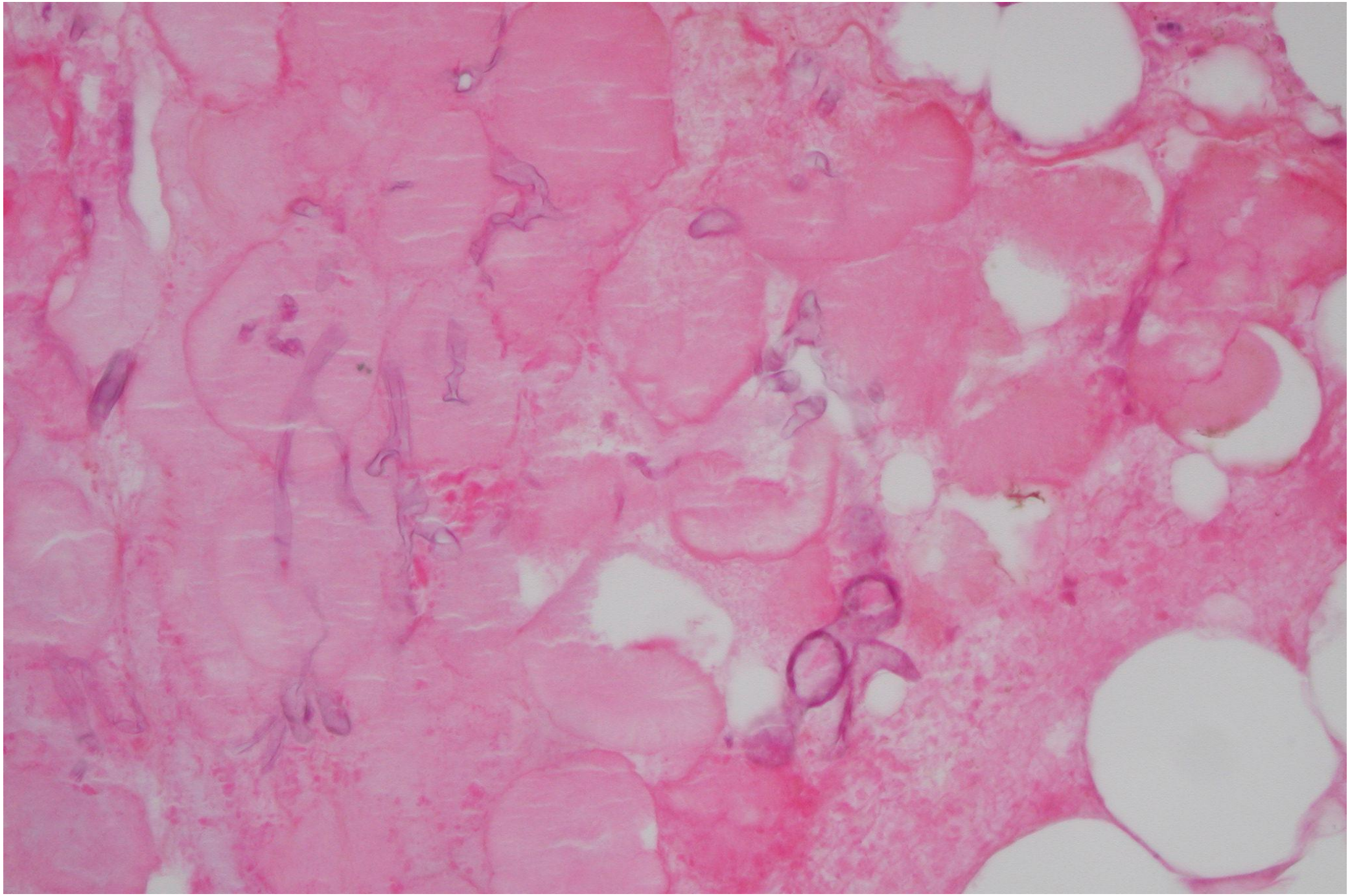


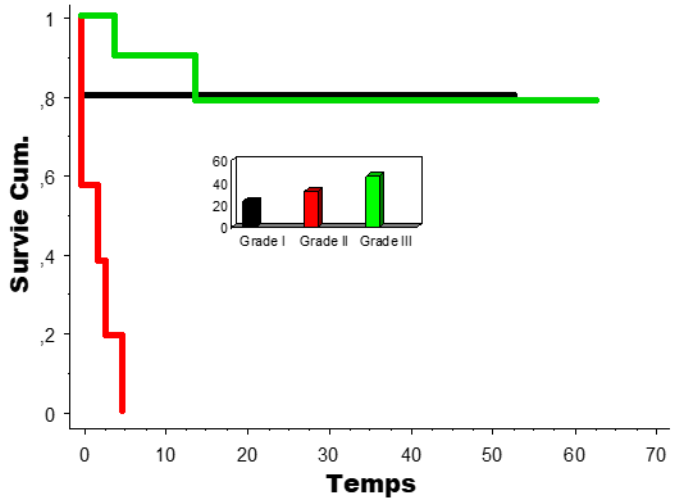
Patterson et al. Clin Infect Dis 2016
Millon et al. J Fungi. 2019
Millon et al. Clin Infect Dis 2022



TREATMENT

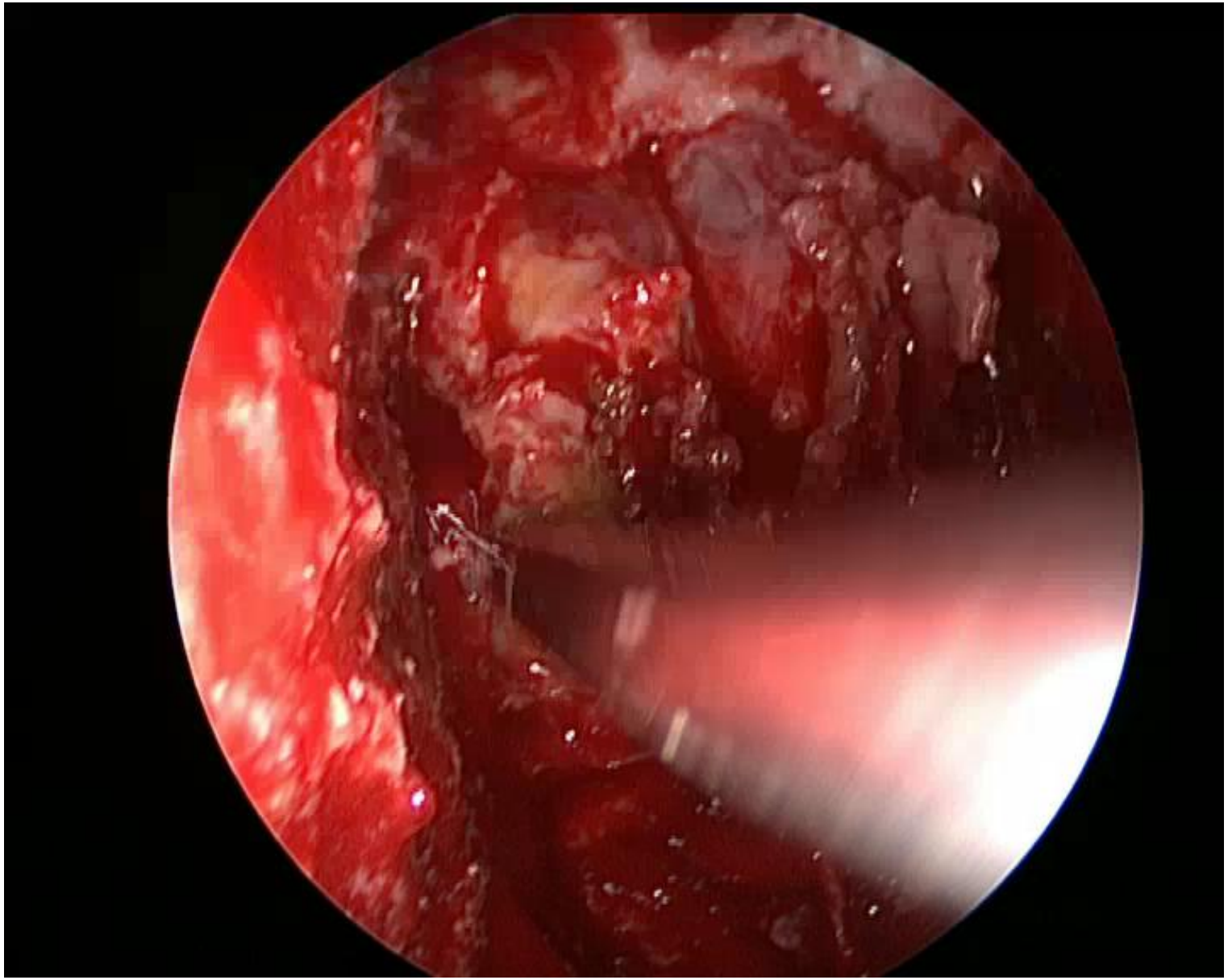
- **MULTIDISCIPLINARY discussion**: surgeons (ENT/neurosurgeon) + infectiologists + physicians that follow the patient for the underlying condition (endocrinologists, nephrologist, hematologist…)
- If possible, **reversal of risk factors and underlying condition**

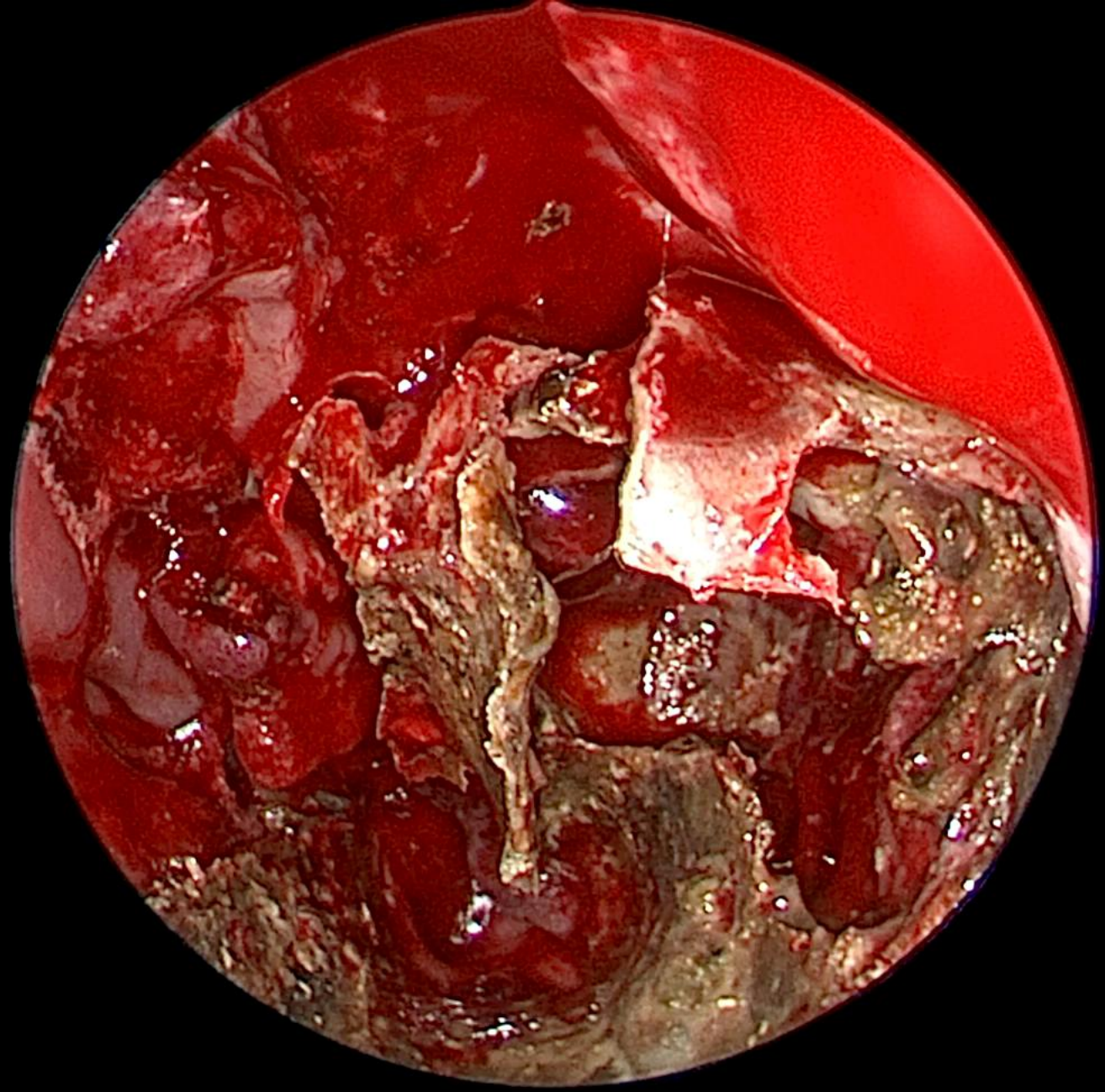
- **Systemic antifungal therapy**, adapted to the antifongigram
  - High-dose liposomal amphotericin B in mucormycosis (then switch to posaconazole; natural resistance to voriconazole)
  - voriconazole in invasive aspergillosis with meningeal involvement
- Start treatment **as early** as possible



- **Surgical treatment**:
  - Mucormycosis: surgical debridement of all necrotic tissues, repeated surgeries if needed
  - Invasive aspergillosis: 2nd line only

Patterson et al. Clin. Infect. Dis. 2016;63:433–442.
Skiada et al. Haematologica 2013;98:492—504.
Lanternier et al. Clin Infect Dis 2012;54:35—43.
Vironneau et al. Clin Microbiol Infect 2014;20:336—9.



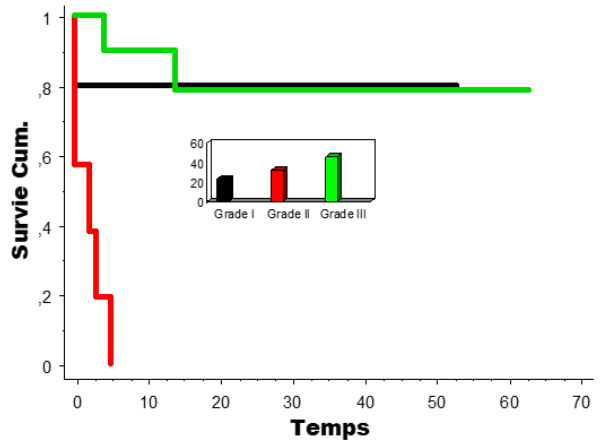


IN CASE OF MUTILATING SURGERY:
MULTIDISCIPLINARY DISCUSSION
(UNDERLYING CONDITION++)

FOLLOW-UP AND PROGNOSIS

- **CLOSE FOLLOW-UP**:
  - Endoscopic examination/imaging at 7, 15, 30 days
  - Residual plasmatic voriconazole
  - Treatment total duration: usually 6-12 weeks
  - Criteria for treatment cessation: clinical + radiological assessment + correction of underlying risk factors

- **3 months-mortality rate:**
  - **Invasive aspergillosis: 21% (51% in case of intracranial invasion)**
  - **Mucormycosis: 25% (56% in case of intracrnial invasion)**



Lanternier et al. Clin Infect Dis 2012
Vironneau et al. Clin Microbiol Infect 2014
Turner et al. The Laryngoscope. 2013
Serris et al. J Infect.2022

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