# Fungal Rhinosinusitis: Snapshot

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# Rhinosinusitis – fungus as a cause

- Fungus as etiology – **Provocative statements**
  - ‘All CR
  - Then, 1
  - ‘A small ple

While the debate continues, let us see - what is the magnitude of the problem

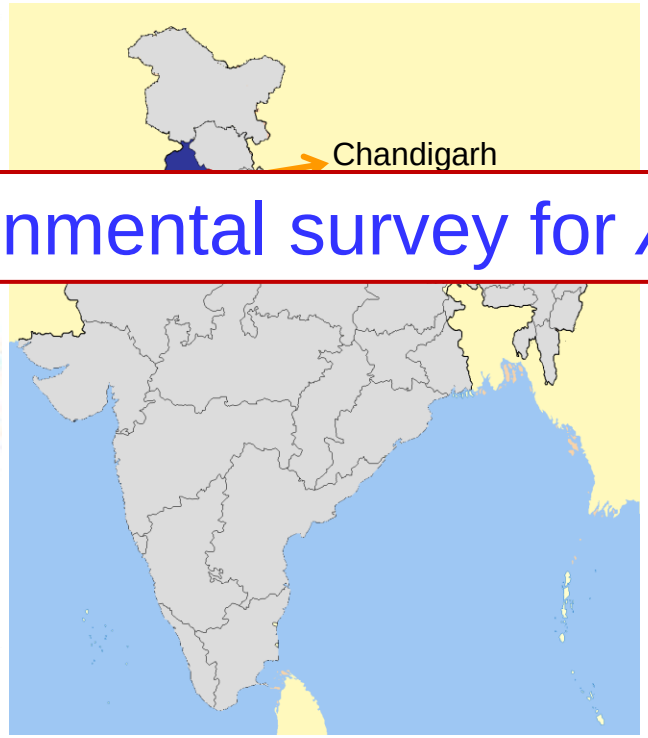
# Prevalence study in north Indian villages

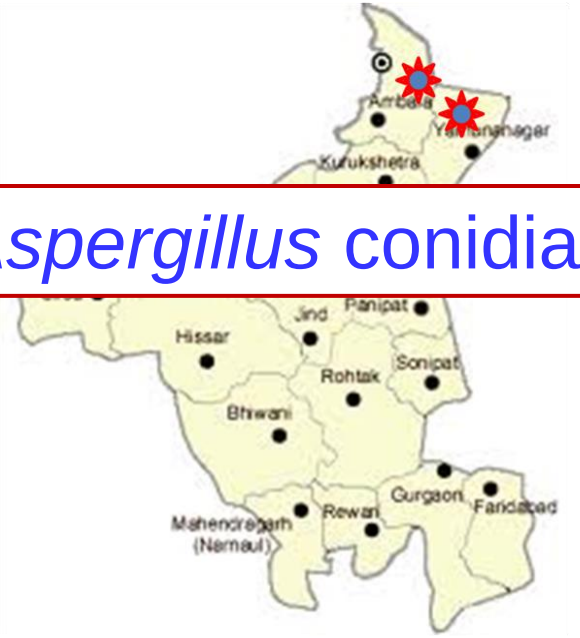
**Chakrabarti A, *et al*. Mycoses 2015, 58: 294**

- Symptoms & signs **>12 weeks**, at least **1 major & 1 minor**
- **Major**: facial pain/pressure, facial congestion/fullness, nasal obstruction/blockage, nasal discharge/purulence/post-nasal drip
- **Minor:** headache, fever, fatigue, dental pain, cough, ear pain/pressure

We also did environmental survey for *Aspergillus* conidia


Punjab




Haryana

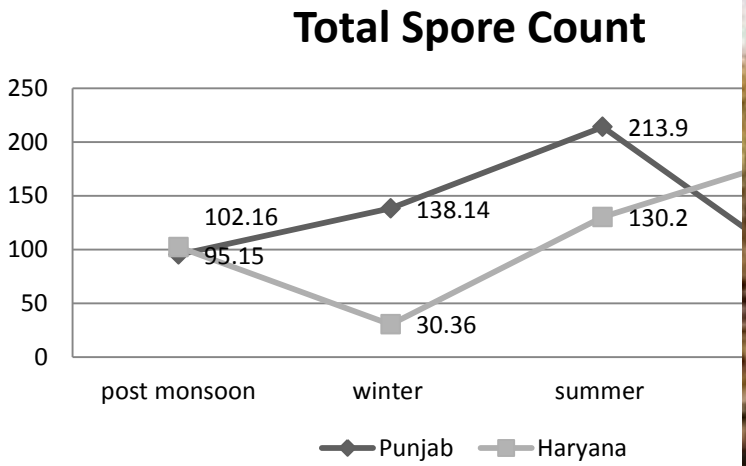
# Prevalence study in north Indian villages

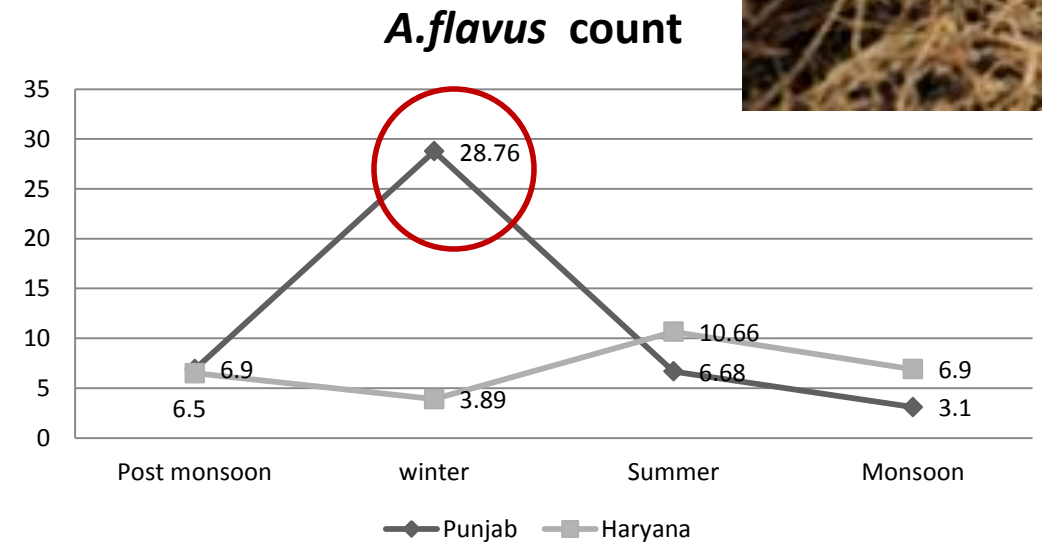
Fig 4

- **Point prevalence**
  - **1.4% young adult suffer from CRS**
- **Prevalence of FRS –**
  - **0.11% of population**
  - **8.1% of all cases of CRS**

- 1 in 1,000 suffer from fungal rhinosinusitis in north India villages

# Fungal conidia in air in north Indian villages




- **44.2% acquired the infection in winter months**

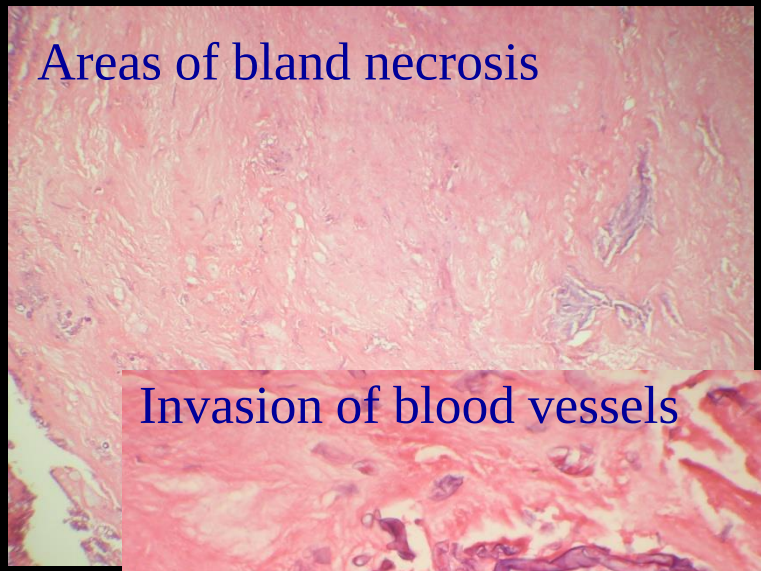
# Categorization of fungal rhinosinusitis

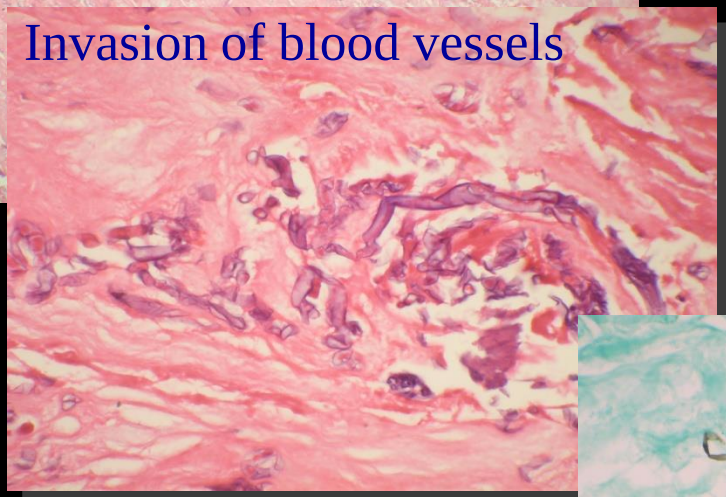
# Categorization of fungal rhinosinusitis (FRS)

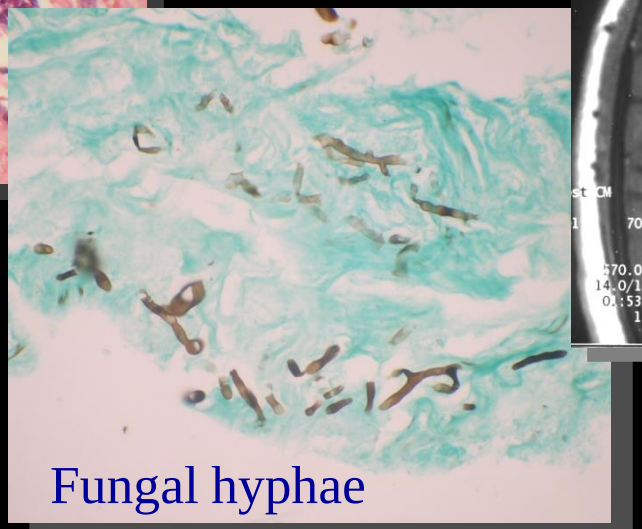
Based on histopathology, clinical findings, laboratory investigations

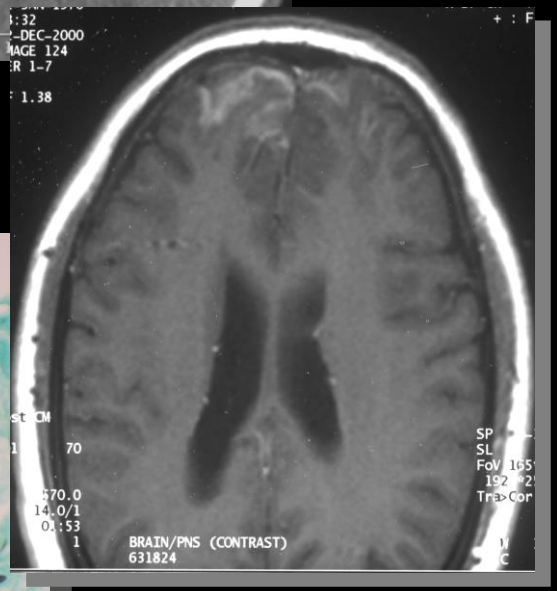
- Invasive
  - Acute invasive (necrotizing/fulminant)
  - Chronic invasive
  - Granulomatous
- Non-invasive
  - Fungal ball (sinus mycetoma)
  - Eosinophil related FRS including AFRS
  - ? Sino-bronchial allergic (SAM)

# Acute invasive FRS



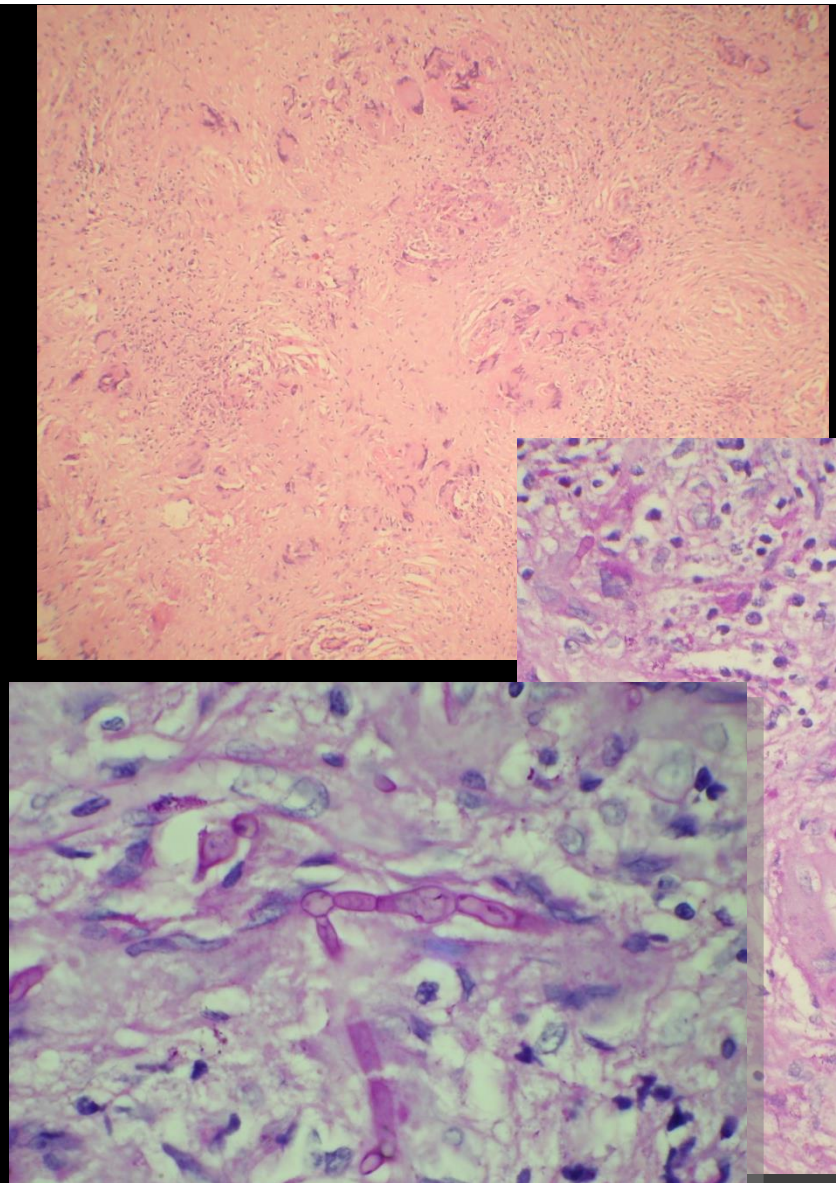



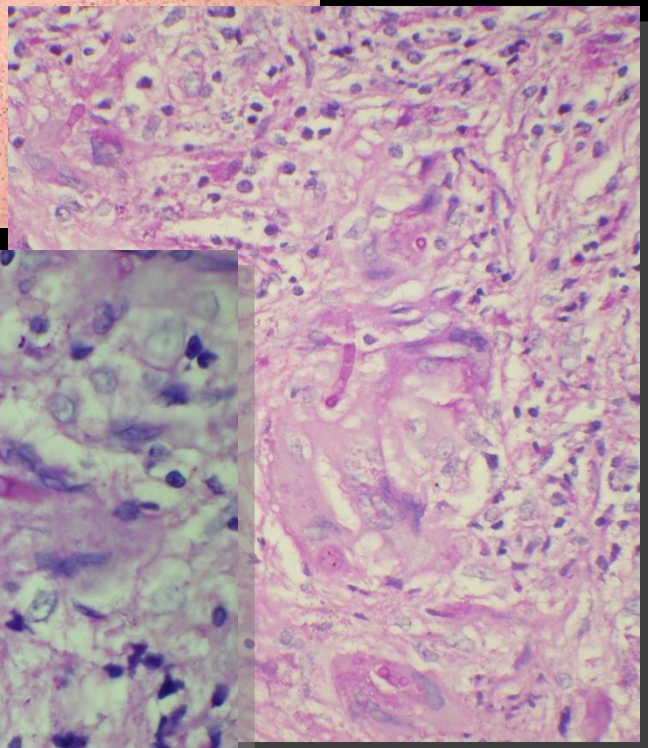



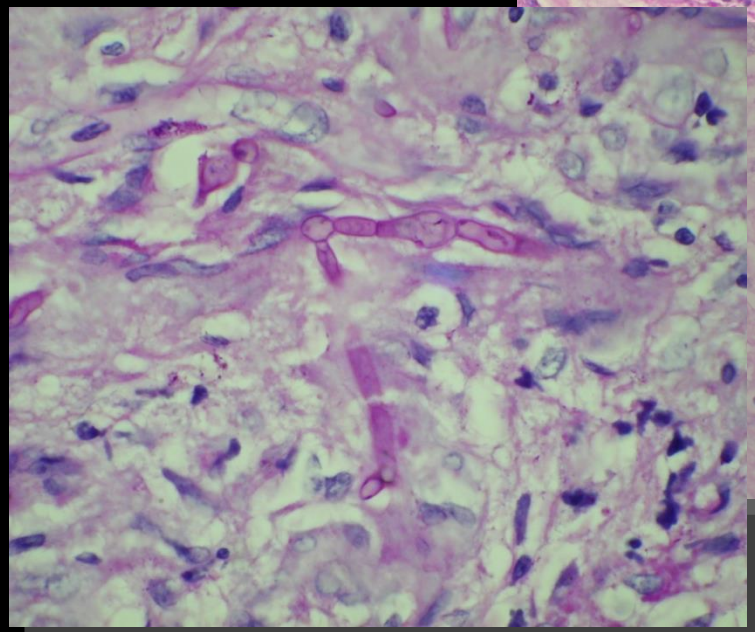



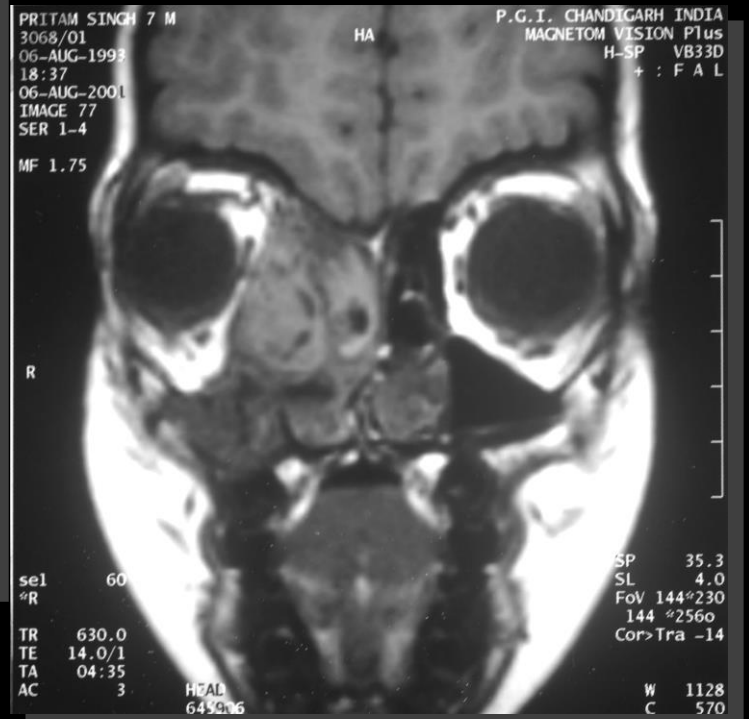
# Granulomatous Invasive

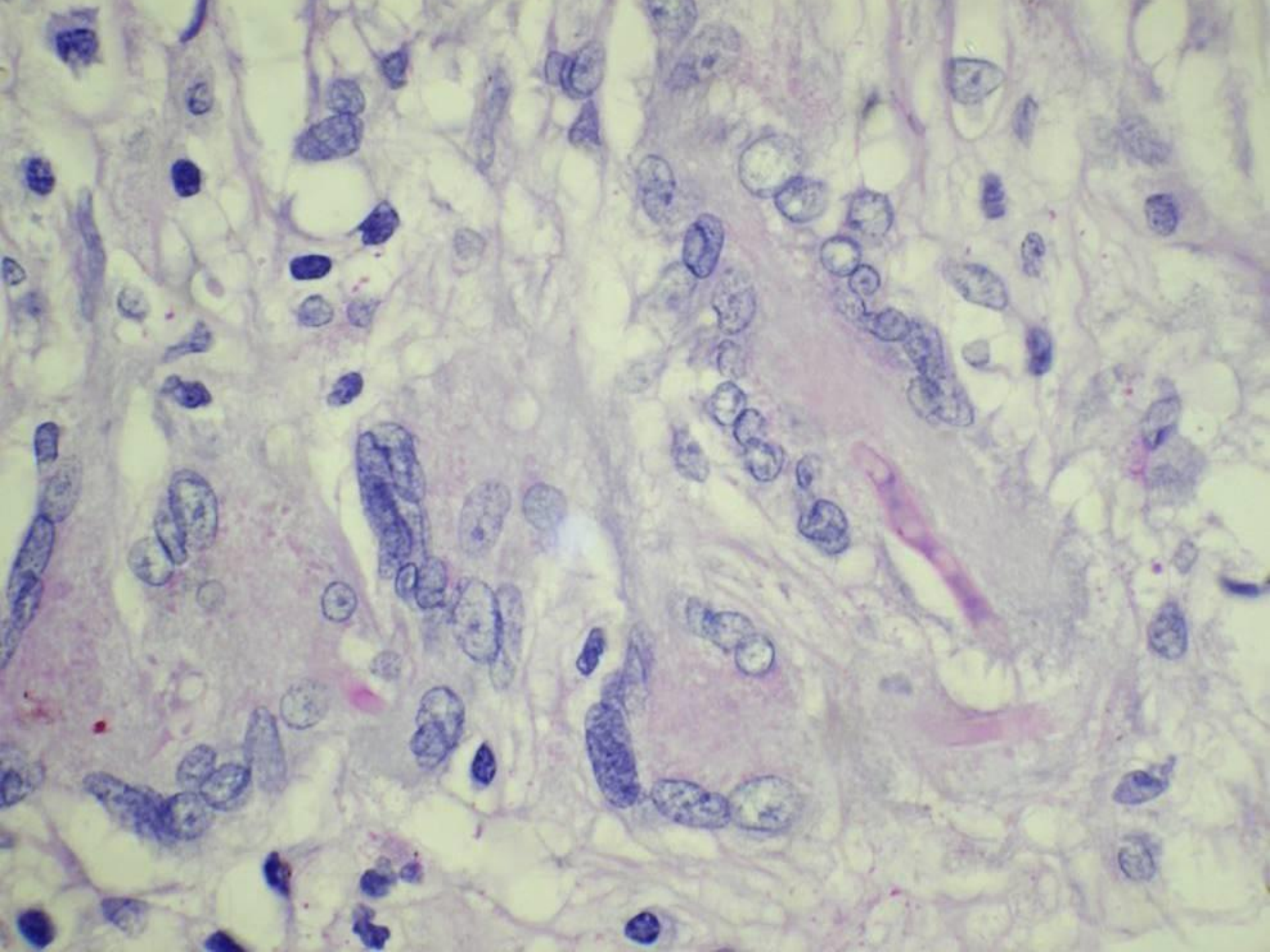
Granulomas with few fungal hyphae
chronic inflammatory infiltrate

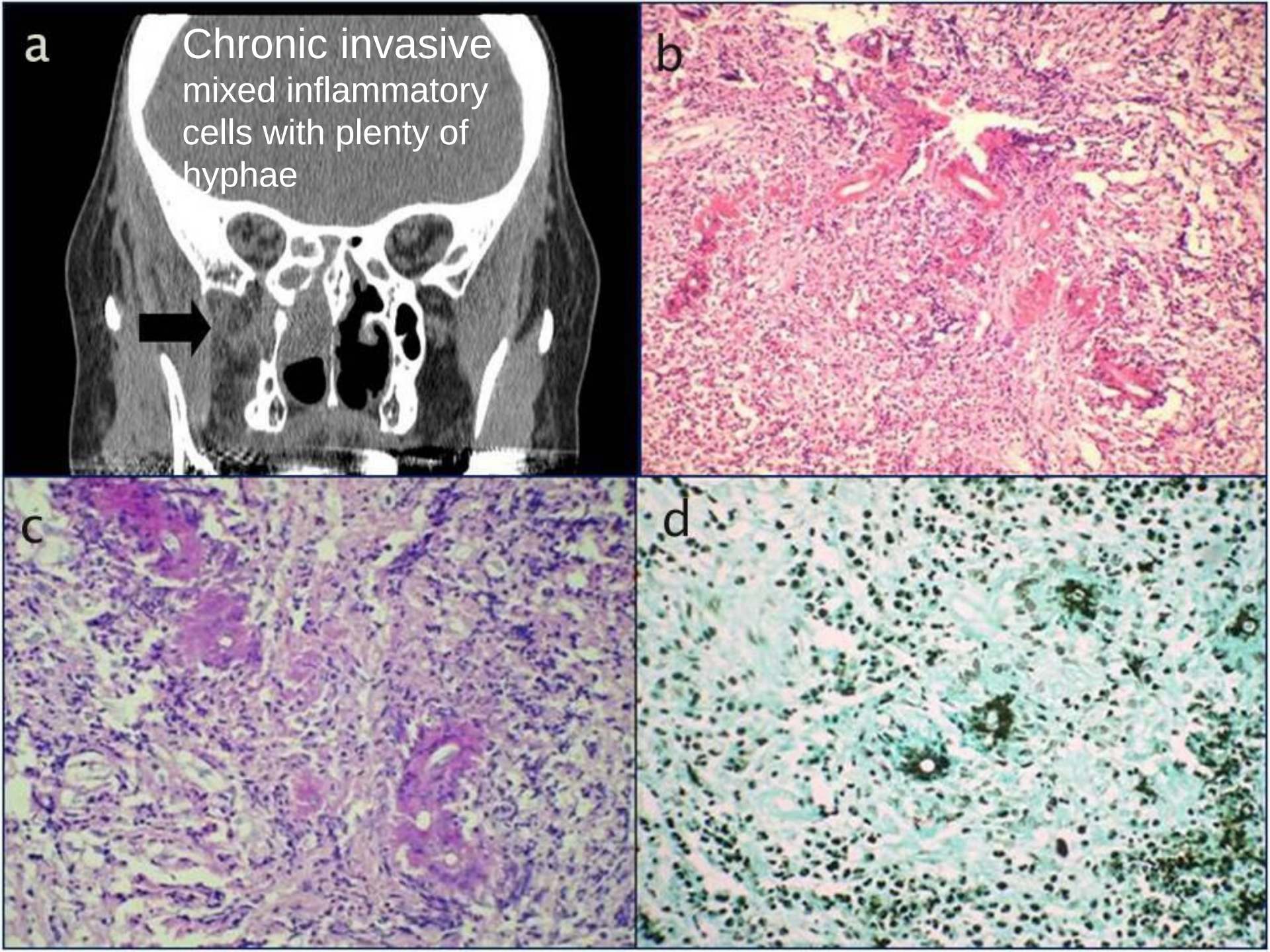










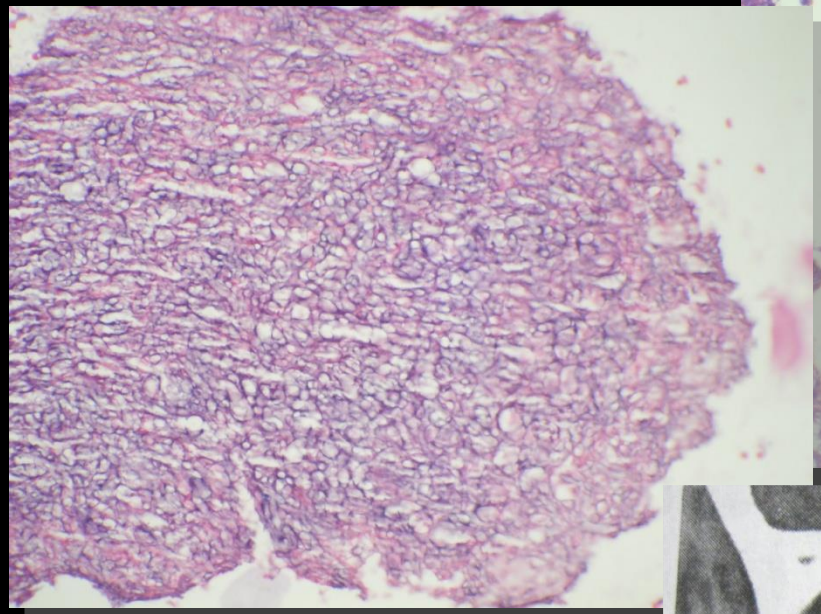

a
Chronic invasive
mixed inflammatory
cells with plenty of
hyphae
b
c
d

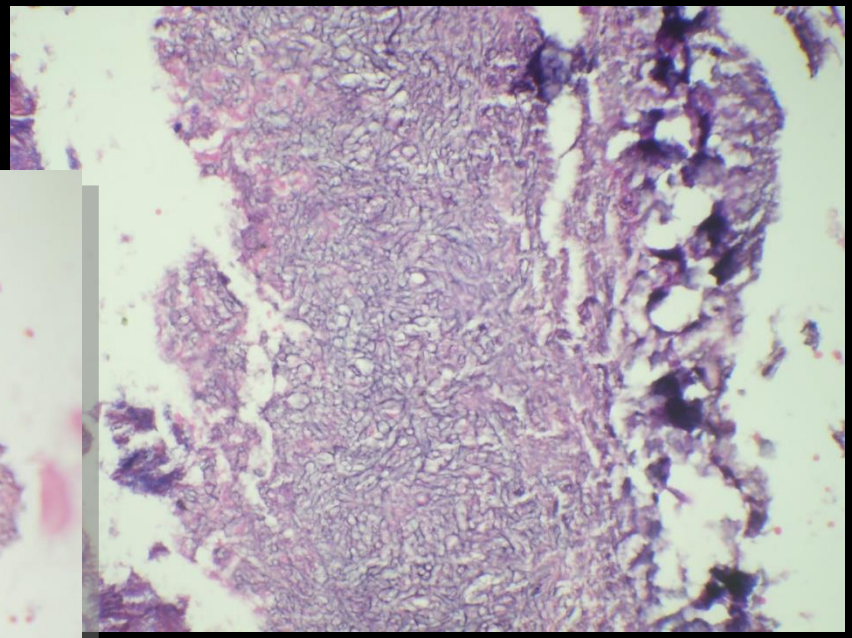
# Difference - granulomatous & chronic invasive

| Characters | Granulomatous | Chronic invasive |
|---|---|---|
| Host | Immunocompetent | Mild diabetes, steroid |
| Geographic location | India → Sudan | Worldwide |
| Presentation | Proptosis | Orbital-apex syndrome |
| Pathology | Granuloma with giant cells; few hyphae | Mixed inflammatory, necrosis of mucosa/ sub-mucosa; plenty of hyphae |
| Mucosal invasion | Yes | Yes |
| Fungi | *A. flavus* | *A. fumigatus* |

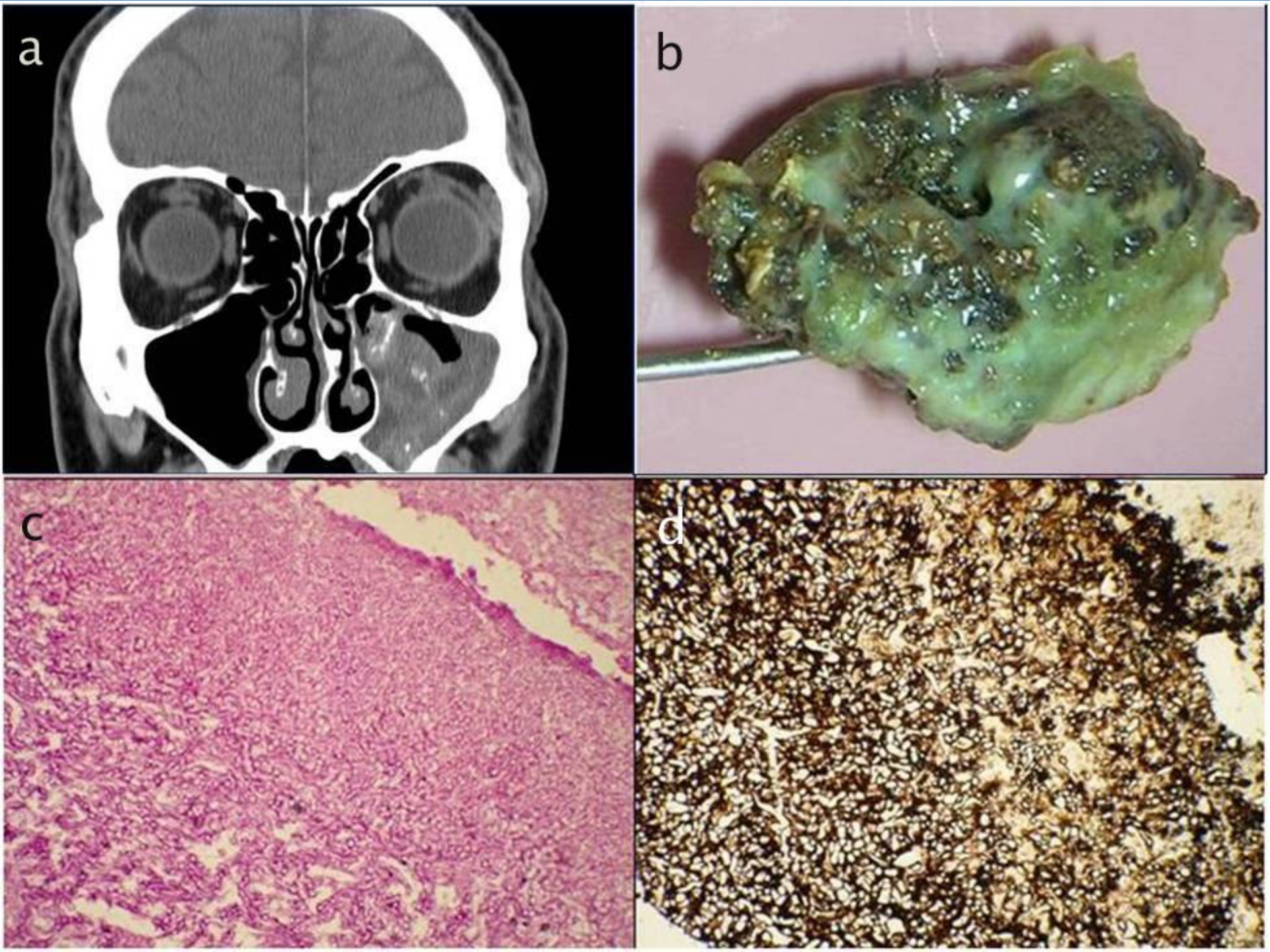
deShazo *et al.*, Arch Otolaryngol Head Neck Sur1997; 123: 1181-8

# Fungal ball





- Usually unilateral
- Involves the maxillary sinus
- Well defined, high attenuation mass
- Occasional flocculent Ca
- Reactive sclerosis of sinus wall
- No invasion


a
b
c
d

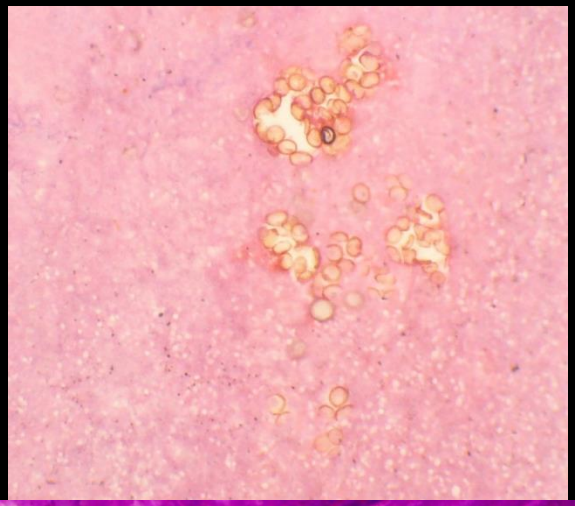
# Eosinophil related FRS (the controversial area)

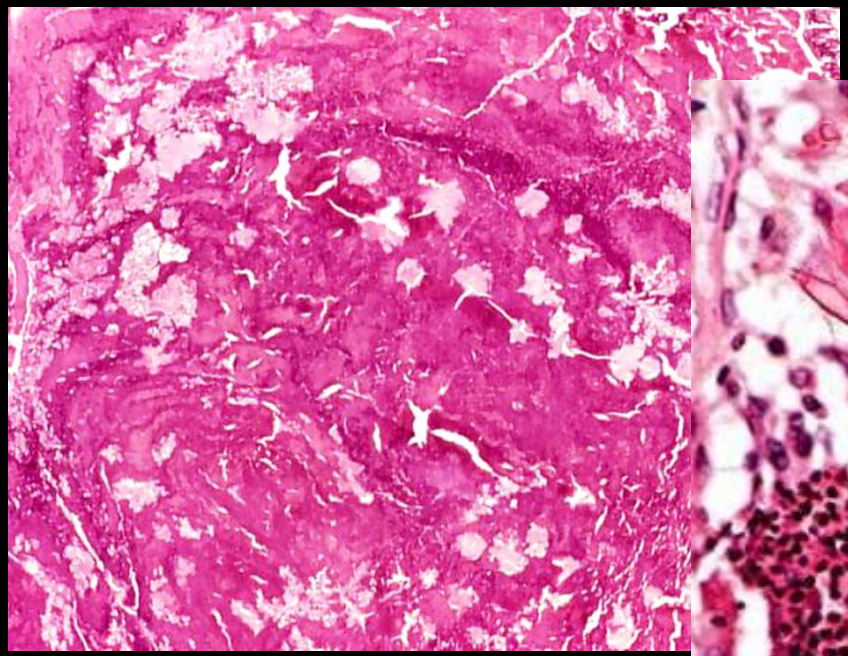
- **Allergic Fungal Rhinosinusitis (AFRS)**
- **Eosinophilic Fungal Rhinosinusitis (EFRS)**
- **Eosinophilic Mucin Rhinosinusitis (EMRS)**

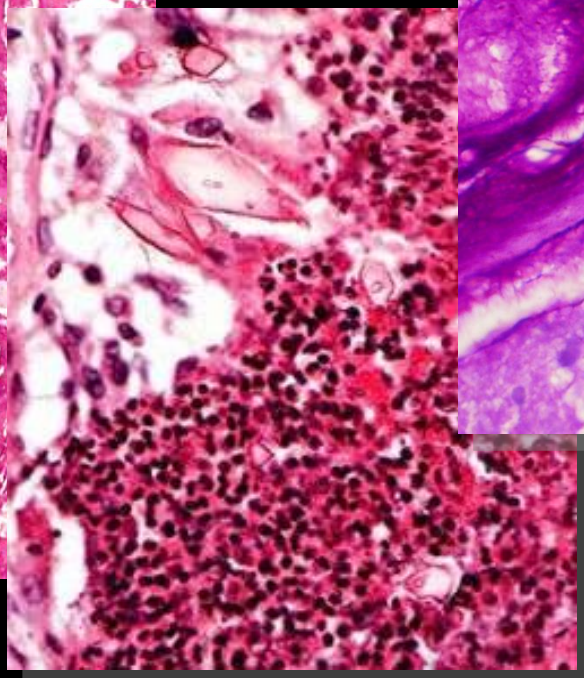
# Allergic fungal rhinosinusitis

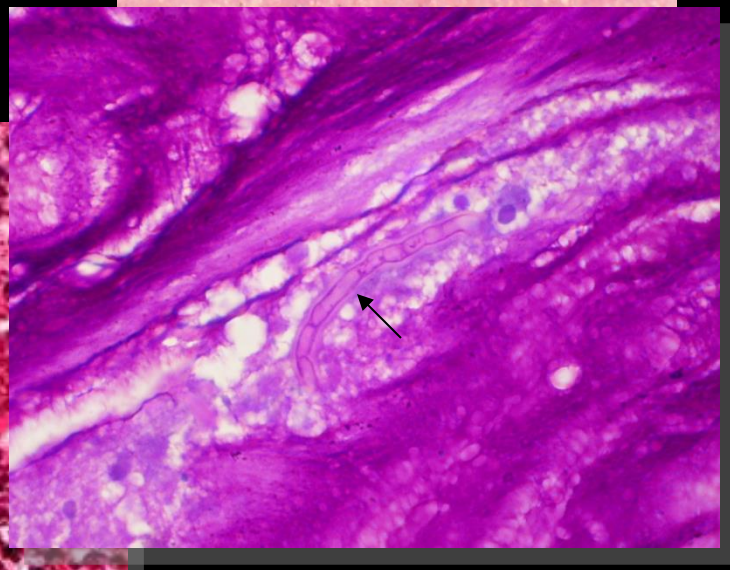
- Type I hypersensitivity
- Nasal polyposis
- Characteristic CT findings
- Allergic mucin without mucosal invasion
- Positive fungal culture of sinus content

Bent & Kuhn, Otolaryngol Head Neck Surg, 1994; 111: 580-8

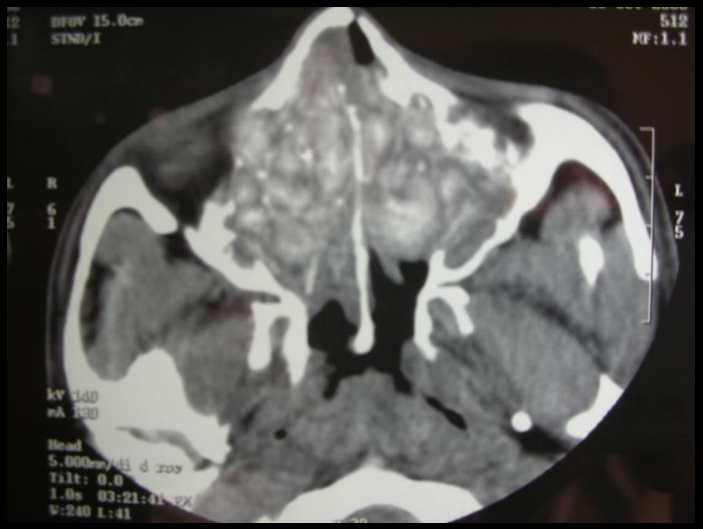








# CT findings in AFRS

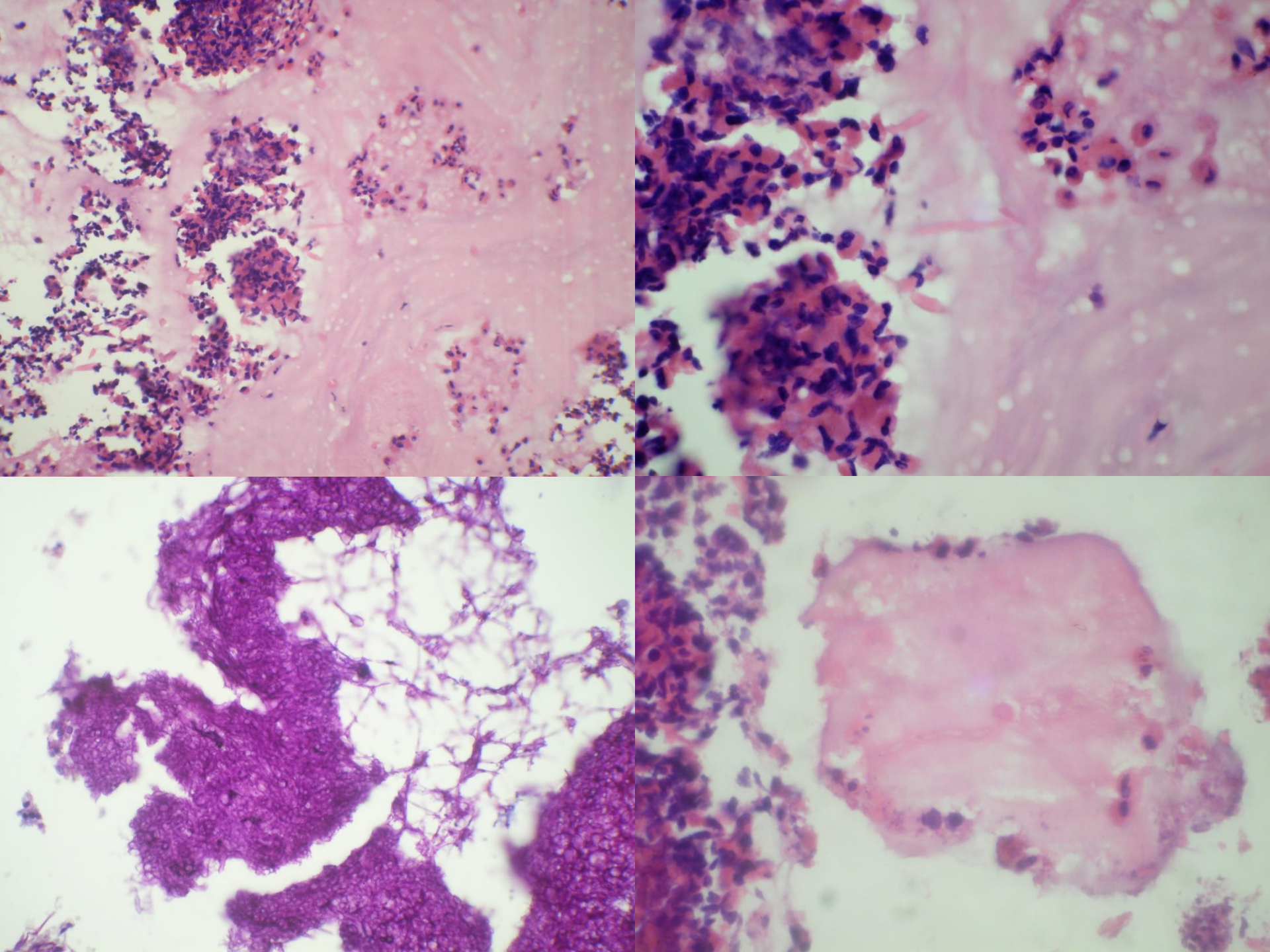


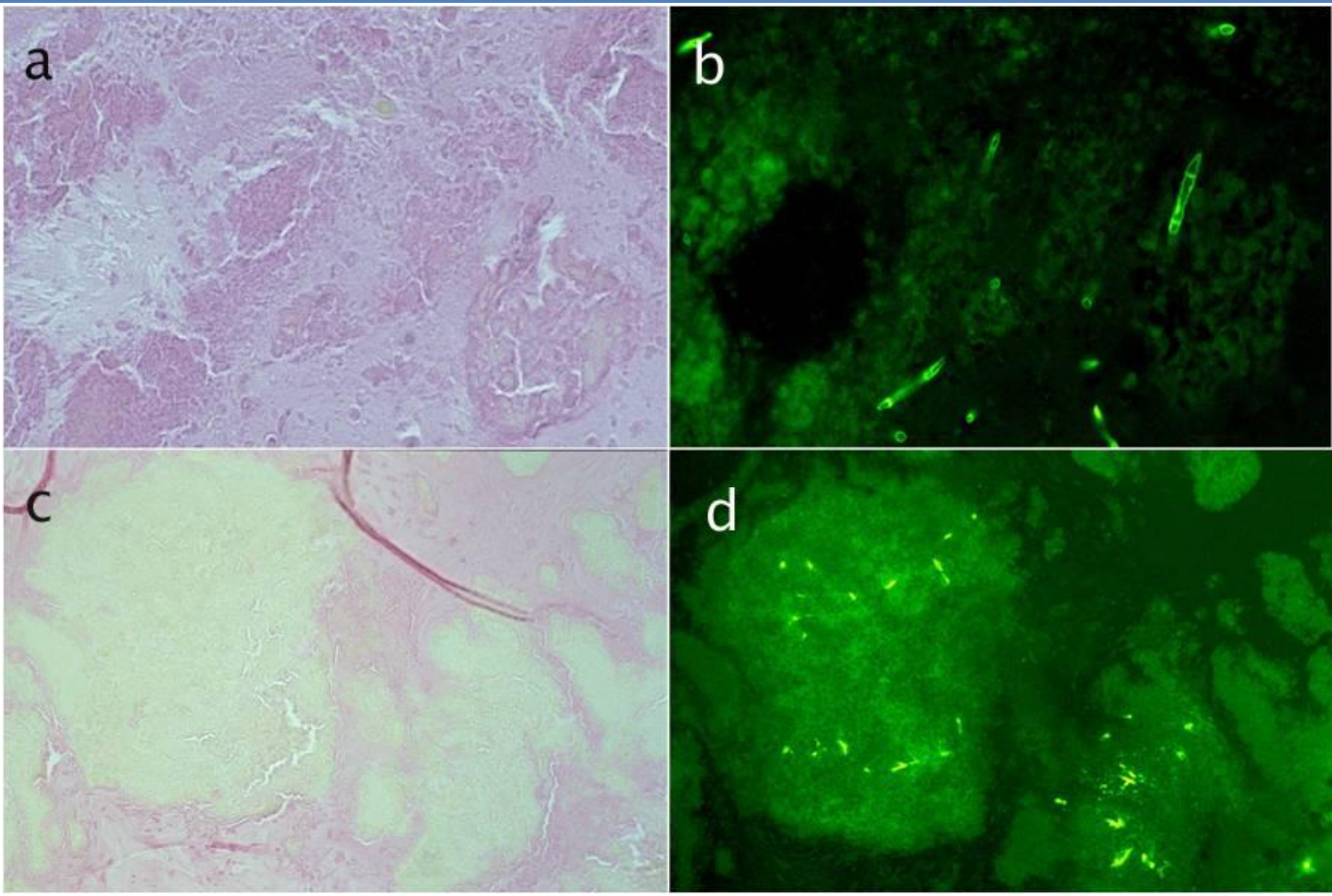
COTTONWOOL PATTERN

CONCRETION PATTERN

HOMOGENOUS NON DENSE PATTERN

HOMOGENOUS GROUND GLASS PATTERN



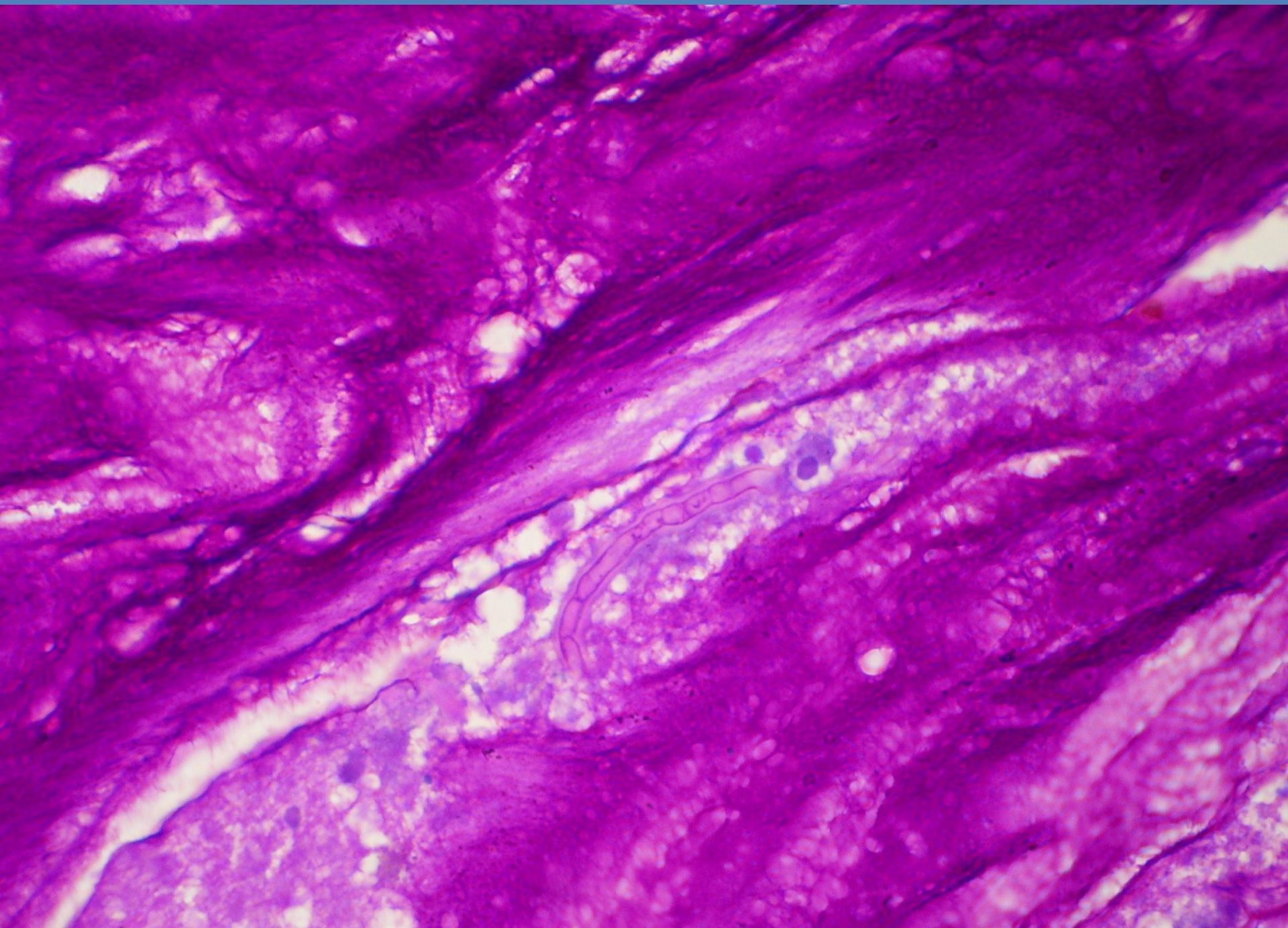

a
b
c
d

# Eosinophilic Fungal Rhinosinusitis (EFRS)

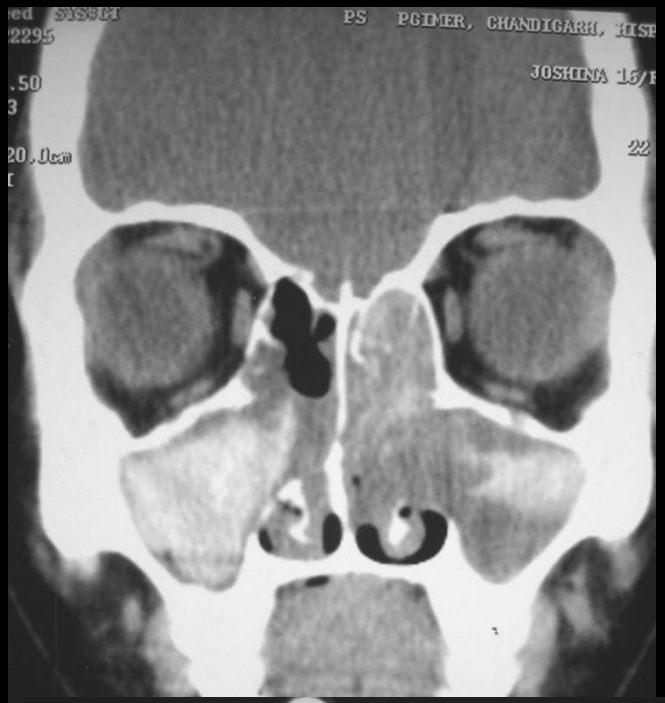
- Subsequently Ponikau *et al.*, J Allerg Clin Immunol 2003; 112: 877-82
  - demonstrated toxic major basic protein (MBP) from eosinophil in mucus of patients with CRS
  - the level of MBP was very high (↑↑toxic level)
  - that could damage nasal epithelium & predisposed bacterial infection
- Therefore, the question remains whether
  - AFRS, a distinct entity, that requires presence of eosinophilic mucin, hyphae & atopy
  - EFRS – a non-allergic fungal eosinophilic inflammation, leads to secondary bacterial infection (most cases CRS)

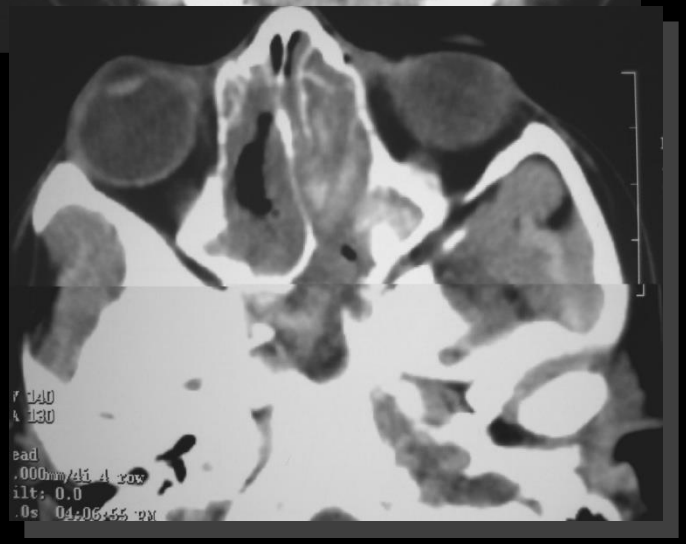
# Eosinophilic mucin rhinosinusitis (EMRS)

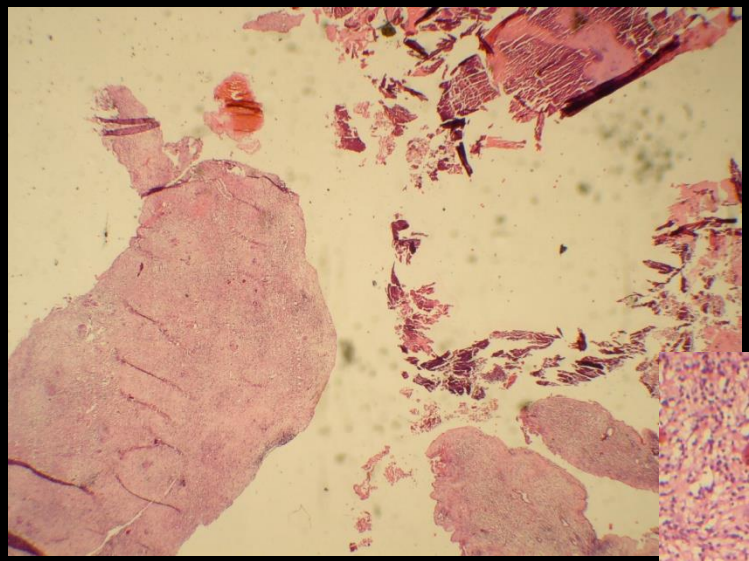
- Proposed by Ferguson, Laryngosocope 2000; 110: 799-813
  - **Eosinophilic mucin present without fungus**
  - A systemic disease with dysregulation of immunological control
  - Significantly associated with asthma, ↑incidence of aspirin sensitivity, ↑incidence of IgG1 deficiency
  - Though systemic steroid could be useful, fungal immunotherapy & antifungal agents would be ineffective

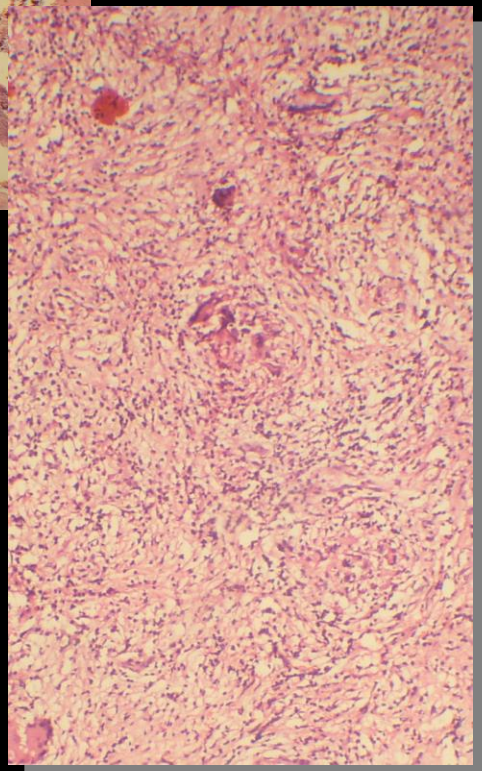


# Allergic fungal rhinosinusitis
# ? invasive







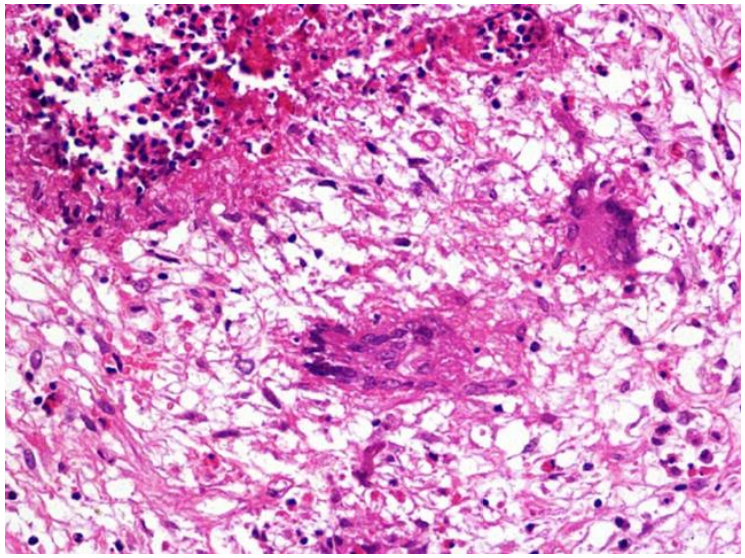
- In 2007, 6 of 105 AFRS cases –Mixed reaction (our experience)

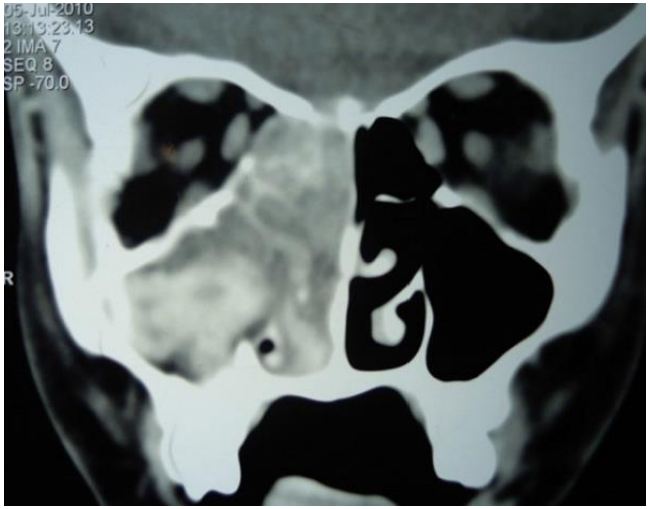
- In 2004, 6 (21%) cases of mixed reaction (New Delhi experience)

# Allergic fungal rhino sinusitis with granulomas: A new entity?

*Medical Mycology*, 2015, 53, 569–575

Rijuneeta Gupta[1,*], Ashok K. Gupta[1], Sourabha Kumar Patro[1], Jagveer Yadav[1], Arunaloke Chakrabarti[2], Ashim Das[3] and Debajyoti Chatterjee[3]





| | Group 1 (AFS+ Granuloma) | group 2 (AFS) | *P* Value |
|---|---|---|---|
| No. of patients | 9 | 48 | |
| Age | 15 to 32 | 12 to 57 | |
| Gender(m:f) | 05:04 | 16:32 | 0.205 |
| h/o atopy | 6 | 9 | 0.003 |
| Nasal obstruction | 9 | 48 | |
| Nasal polyps | 9 | 48 | |
| Nasal Discharge | 8 | 43 | |
| Post nasal Drip | 7 | 44 | |
| **Clinical features suggestive of aggressive/ invasive disease** | | | |
| Headache | 6 | 29 | |
| Facial pain | 2 | 4 | |
| Proptosis | 5 | 15 | 0.161 |
| Telecanthus | 9 | 16 | 0.000 |
| Diplopia | 5 | 4 | 0.000 |
| **Radiology** | | | |
| Multiple sinus involvement | 9 | 48 | |
| Bony expansion | 9 | 39 | 0.157 |
| Hyperdensiy | 9 | 48 | |
| Intraorbital (IO) | 8 | 11 | 0.000 |
| Intracranial (IC) | 4 | 9 | 0.092 |
| Extrasinus (IC or IO) | 9 | 12 | 0.000 |
| Eosinophilia (AEC >500/$\mu$l) | 6 | 28 | 0.640 |

# AFRS vs. EFRS - Controversy

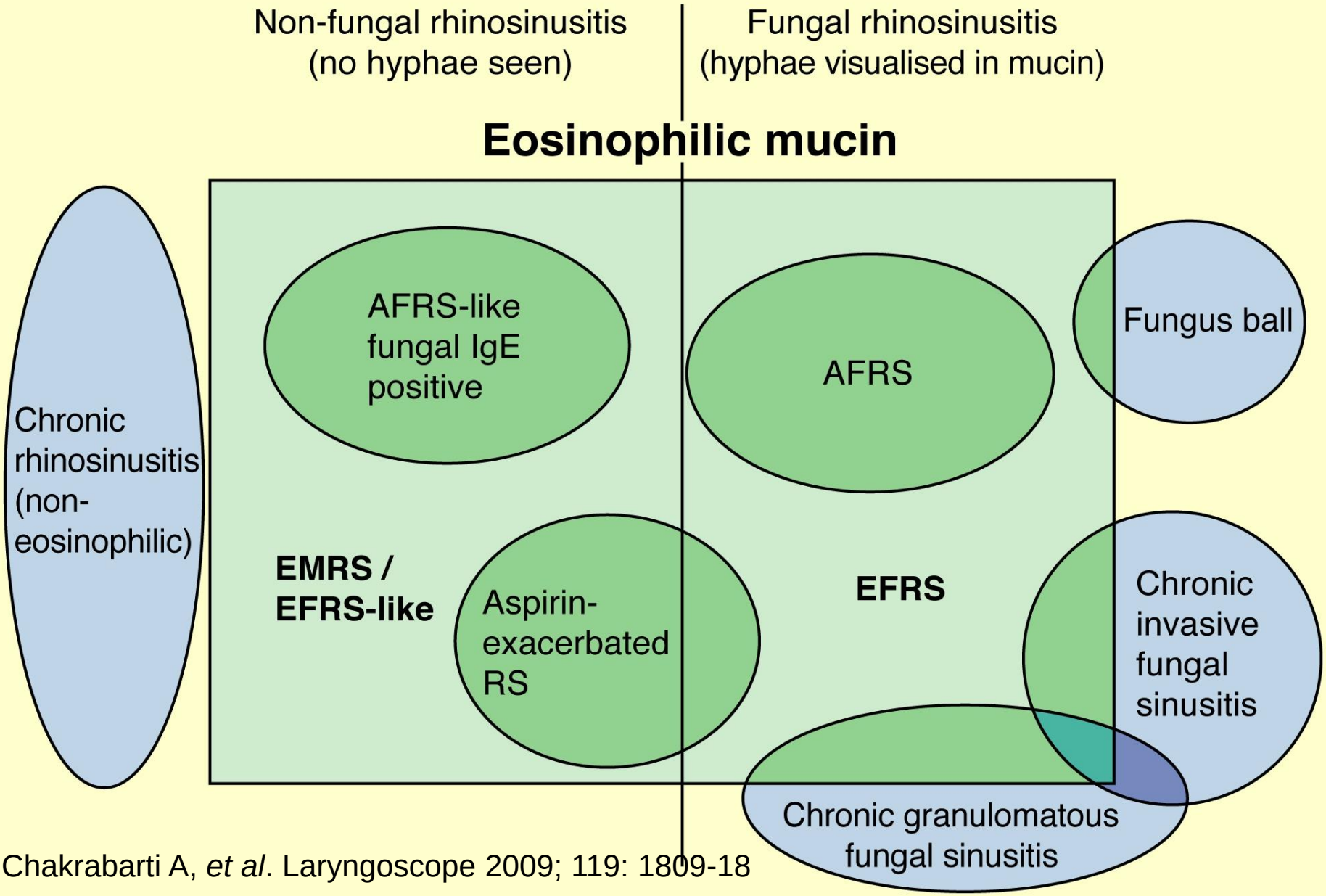
- Is it a systemic allergic disease?
- Is it a localized allergic disease?
- Allergy – not at all

ISHAM
INTERNATIONAL SOCIETY OF HUMAN AND ANIMAL MYCOLOGY

# 11. Working Group on Fungal Sinusitis

- developed a consortium to work together and to exchange ideas for resolving problems in the area of fungal sinusitis
- the network has been named as Fungal Sinusitis Network (FSN) with website http://fungalsinusitisgroup.org/
- the basic aim of our network is to understand the disease and to develop a management protocol

# Chronic rhinosinusitis




Chakrabarti A, *et al*. Laryngoscope 2009; 119: 1809-18

# Management of FRS

- Acute invasive – surgery + amphotericin B + reversal of immunosuppression
- Chronic invasive/ - surgery + ampho B/itraconazole
  Chronic granulomatous
- Localized colonization - ? surgery
- Fungal ball - surgery
- AFRS/EFRS/EMRS - surgery + steroid (local/systemic)
  immunotherapy, avoid allergen

# Summary

| Features | AIFRS | CIFRS | GFRS | Fungal ball | AFRS | EFRS |
|---|---|---|---|---|---|---|
| Host | Immunuo-suppressed | Mild immun-suppressed | Competent | Competent | Atopy | Non-atopic |
| Demography | Any age/sex | Adult | Young adult villagers | Middle & elderly female | Urban in USA, villagers in Asia | Any person |
| Geographic distribution | Worldwide | Worldwide | India, Sudan, Pakistan, Saudi | Worldwide, more common in France | Southwest USA, India, Pakistan | Worldwide |
| Fungi | *Mucor* more common, then *Aspergillus* | *Aspergillus* species | *A. flavus* | *Aspergillus* species | Dematiaceous hyphae in USA, *A. flavus* in India | Dematiaceous hyphae in USA, *A. flavus* in India |
| Role of fungus | Pathogen | Pathogen | Pathogen | Saprobe | Allergen | Not clear |

# Summary

| Features | AIFRS | CIFRS | GFRS | Fungal ball | AFRS | EFRS |
|---|---|---|---|---|---|---|
| Pathology | Acute invasion blood vessels | Mixed reaction, plenty hyphae | Granuloma, scanty hyphae | Dense accumulation of hyphae | Eosinophilic mucin, few hyphae | Eosinophilic mucin, few hyphae |
| Course of disease | Acute <4w | Chronic >12w | Chronic >12w | Chronic >12w | Chronic >12w | Chronic >12w |
| Presentation | Acute, eschar , involvement of eye, brain, face | Ethmoid, sphenoid involvement, orbital extension | One or more sinuses, orbital apex syndrome | Nasal obstruction, facial pain, purulent discharge | Nasal obstruction, facial pain, hyposmia, orbital | Nasal obstruction, rhinorrhoea, facial pain |
| Diagnosis | Endoscopic biopsy, CT | Endoscopic biopsy, CT | Endoscopic biopsy, CT | Endoscopic biopsy, CT | Type I skin test, polyp, eosinophilic mucin, fungi, characteristic CT | Non-allergic eosinophilic mucin, fungi |

# Summary

| Features | AIFRS | CIFRS | GFRS | Fungal ball | AFRS | EFRS |
|---|---|---|---|---|---|---|
| Treatment | Aggressive surgery, amph B, control of immuno-suppression | Surgery, systemic antifungal | Surgery, systemic antifungal | Surgery | Surgery, oral/ or local steroid, ?immunotherapy | Surgery, ?steroid, ?antifungal therapy |
| Prognosis | High morality, fungal emergency | Better prognosis, recurrence may occur | Better prognosis, recurrence may occur | Cure rate good | Recurrence common | Not clear |

# Conclusions

## The case for fungus – unproven (more questions than answers)

- Fungus can cause a variety of conditions in the nose & paranasal sinuses, partly competency of immune system determines severity
- Fungi & eosinophil can be detected in nearly all CRS patients (However, fungi are also present in healthy controls)
- Many mechanisms may be involved for the fungi to cause disease in those individuals (more research required!)
- Definite geographical variation exists in fungi causing CRS & allergy
- Antifungal therapy required for invasive varities
- Antifungal therapy appears to be beneficial in selected group of patients like AFRS (but the effect is not permanent)

# Members of ISHAM Working group on Fungal Sinusitis

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**Thank you!**

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Mohnish Grover, India
Usha Singh , India
Ratna Rao , India
Shesh Rao Nawange , India