

Controversies surrounding categorization of fungal sinusitis

Arunaloke Chakrabarti

**Professor, Department of Medical Microbiology
Center for Advanced Research in Medical Mycology
Postgraduate Institute of Medical Education &
Research, Chandigarh 160012, India**

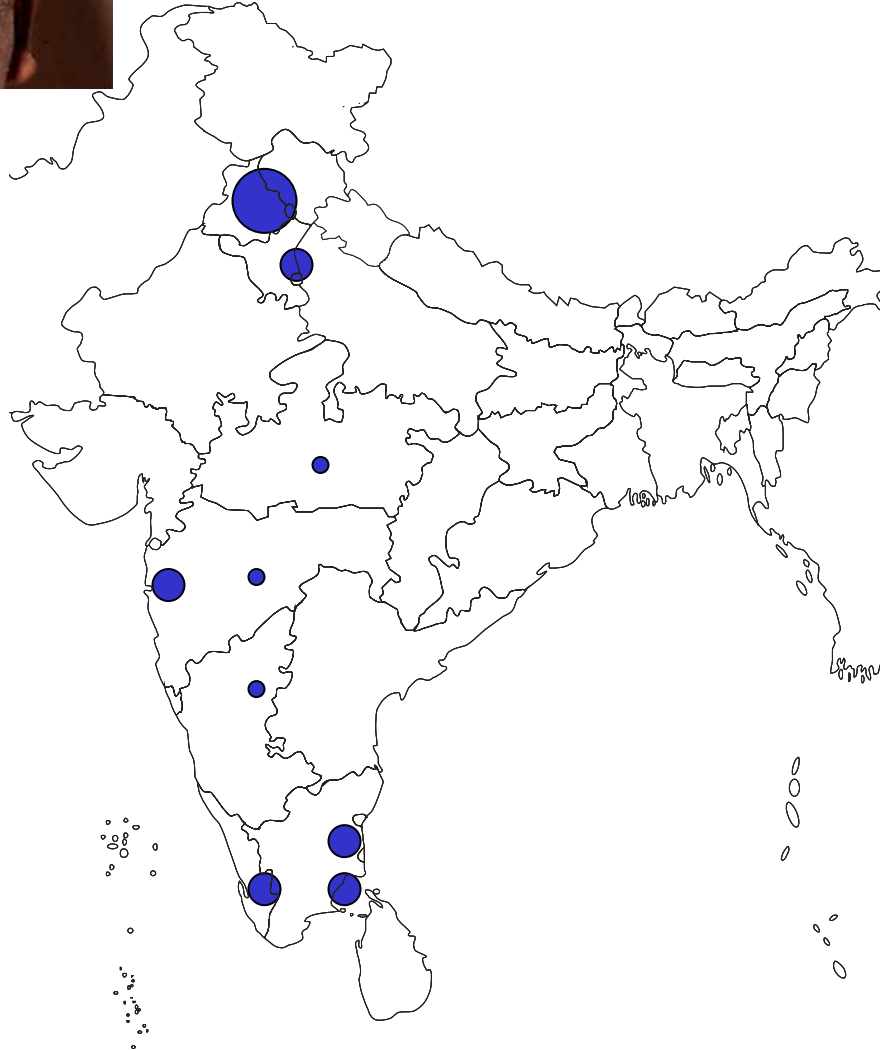


Fungal rhinosinusitis



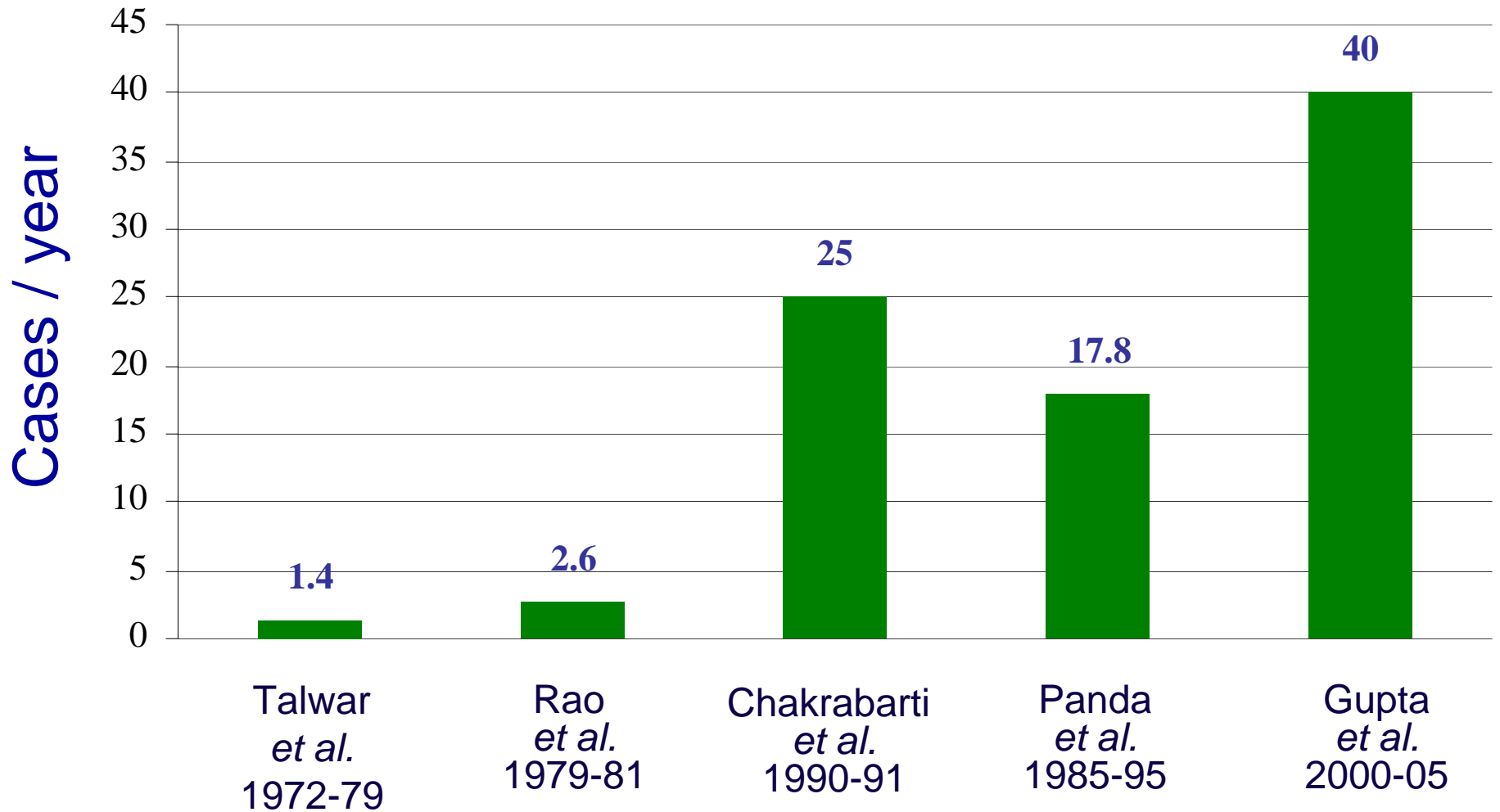
- Once considered a rare disorder, is reported with increasing frequency worldwide
 - Exact frequency not known
 - No population based data
 - No clear-cut systematic hospital based data
- In India, earlier fungal sinusitis were reported only from north India
- At present, increasingly reported from other parts of the country as well

Fungal sinusitis in India



Fungal sinusitis

Our experience



Fungal rhinosinusitis - recent experience

- Period of study – July 2006 – December 2007 (18 months)
- Chronic sinusitis – 148 cases, fungus related – 105 cases
- Fungal rhinosinusitis – 67 cases/year

Category	No. of cases (%)	Fungus isolated (%)	Fungi
AFRS	64 (61)	47 (73)	<i>A. flavus</i> – 45, <i>A. terreus</i> -1, <i>A. niger</i> – 1
Fungal ball	2 (2)	-	-
Granulomatous	17 (16)	9 (53)	<i>A. flavus</i> - 9
Acute invasive	16 (15)	11 (69)	<i>R. arrhizus</i> – 10, <i>A. elegans</i> – 1
Mixed (AFRS + Granulomatous)	6 (6)	6 (100)	<i>A. flavus</i> - 6

Fungus rhinosinusitis - our experience

	1990-91 (2)	1992-96 (5)	1997-98 (2) excluding AFRS	2006-07 (1.5)
No. of cases	50	176	25	105
AFRS (%)	4	7	-	61
Fungal ball (%)	62 (classified as non-invasive)	46	28	2
Chronic invasive / granulomatous (%)	30	31	24	16
Acute invasive(%)	4	7	-	15
Destructive- non- invasive (%)	Not known	9	48	-
Mixed (AFRS + Granulomatous) (%)	-	-	-	6

Consensus on rhinosinusitis

American Academy of Otolaryngology
Head & Neck Surgery & other related
societies – conducted a workshop

- Acute (bacterial) rhinosinusitis
- Chronic rhinosinusitis (CRS) with polyps
- CRS without polyp
- Allergic fungal rhinosinusitis

Categorization of fungal rhinosinusitis

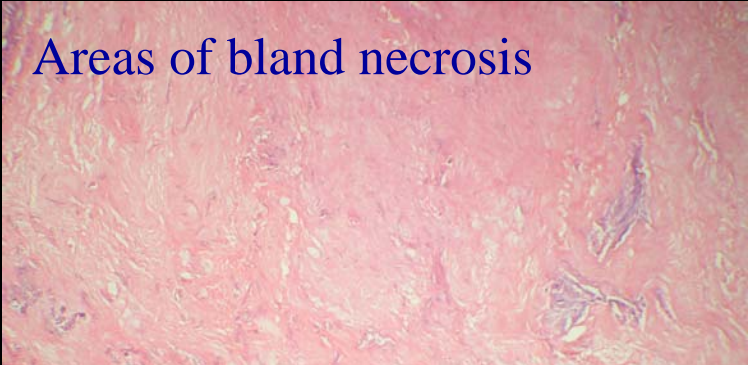
- Two distinct clinical settings
 - Acute invasive in immuno-suppressed
 - Chronic fungal rhinosinusitis in healthy host
- Acute invasive (fulminant) variety – well known to clinicians
- Existing knowledge of chronic fungal rhinosinusitis is controversial & confusing
 - Chronic type is not uniform single entity
 - Acute invasive can turn protracted on therapy
 - Whether fungi can exist in sinus mucus without causing disease

Categorization of fungal rhinosinusitis (FRS)

Based on histopathology, clinical findings, laboratory investigations

- Invasive
 - Acute invasive (necrotizing/fulminant)
 - Chronic invasive
 - Granulomatous (deShazo *et al.*, 1997)
 - Chronic eosinophilic-lymphocytic granuloma (Schubert,2004)
- Non-invasive
 - Allergic
 - Fungal ball (sinus mycetoma)
 - ? Sino-bronchial allergic (SAM)

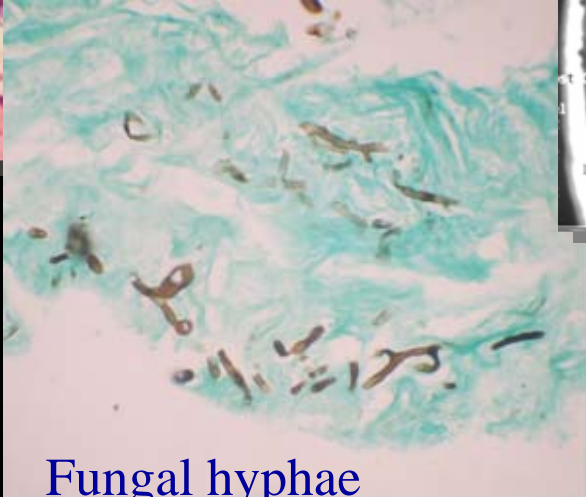
Acute invasive FRS



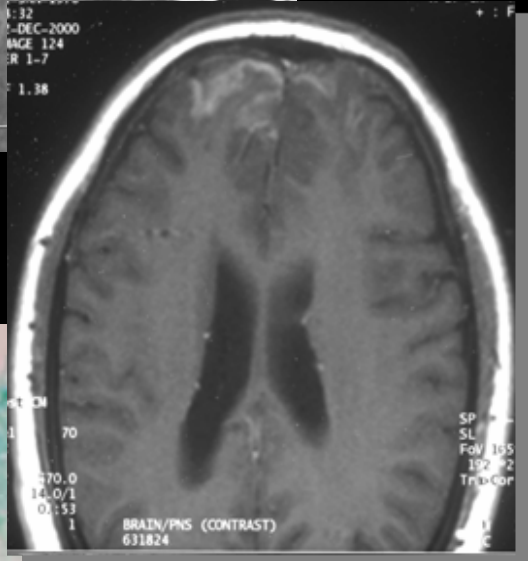
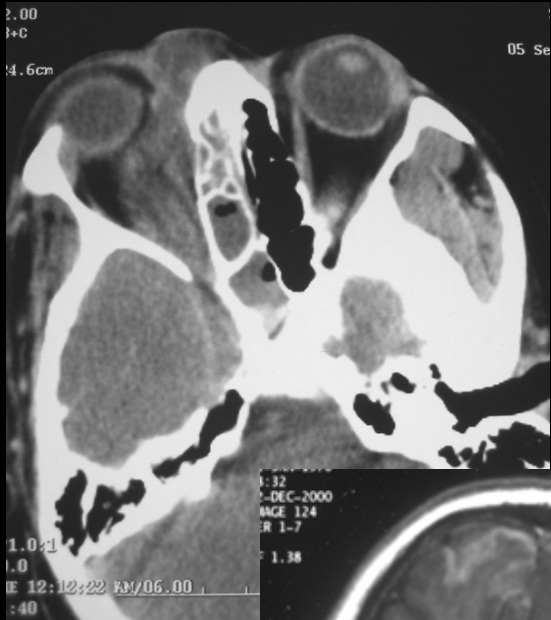
Areas of bland necrosis



Invasion of blood vessels

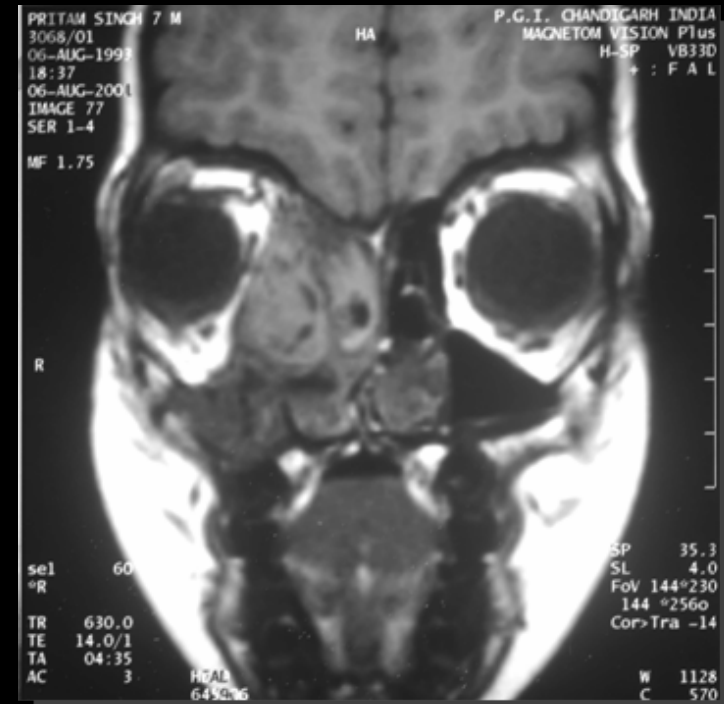
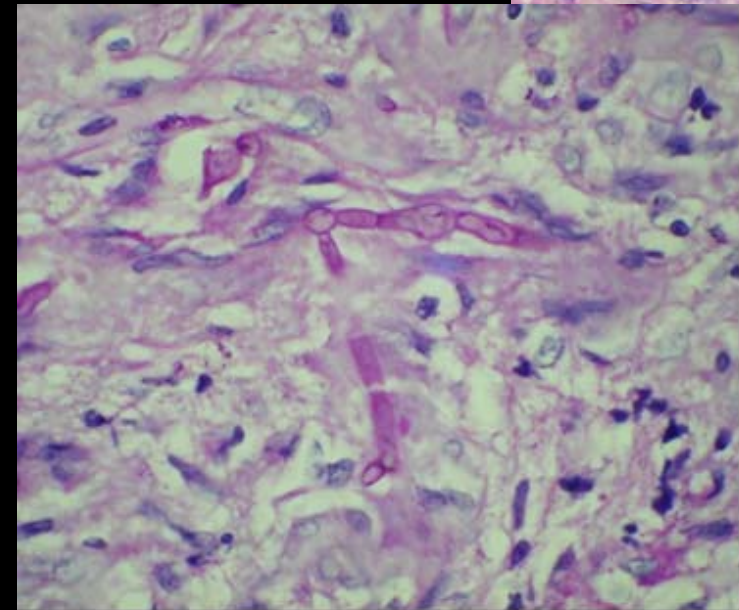
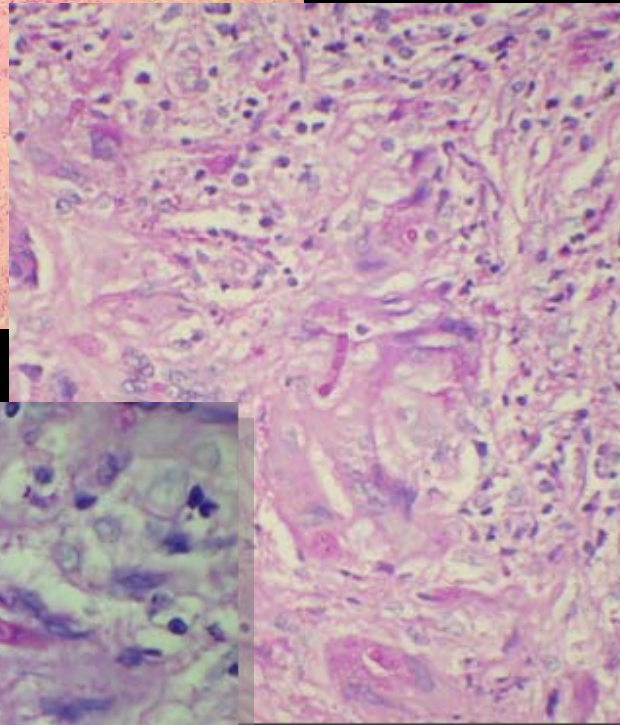
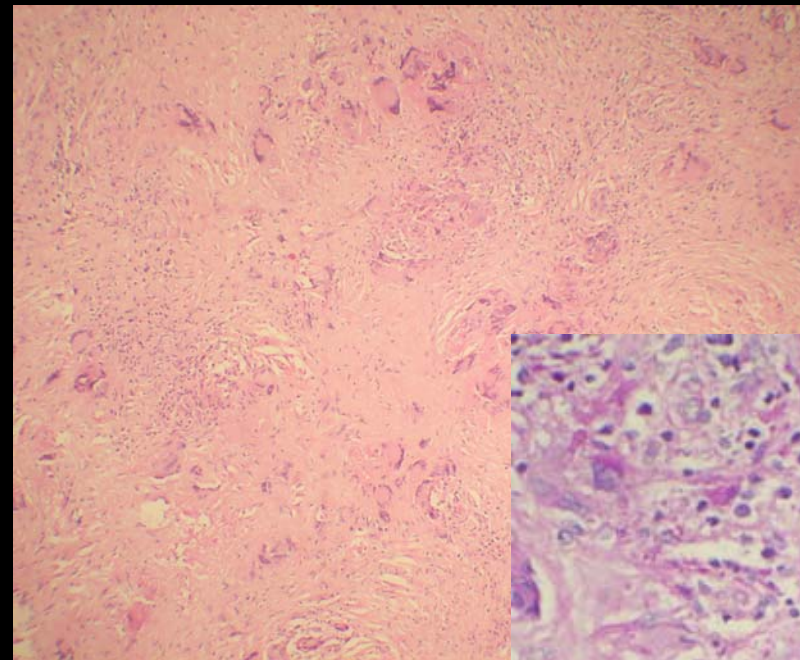


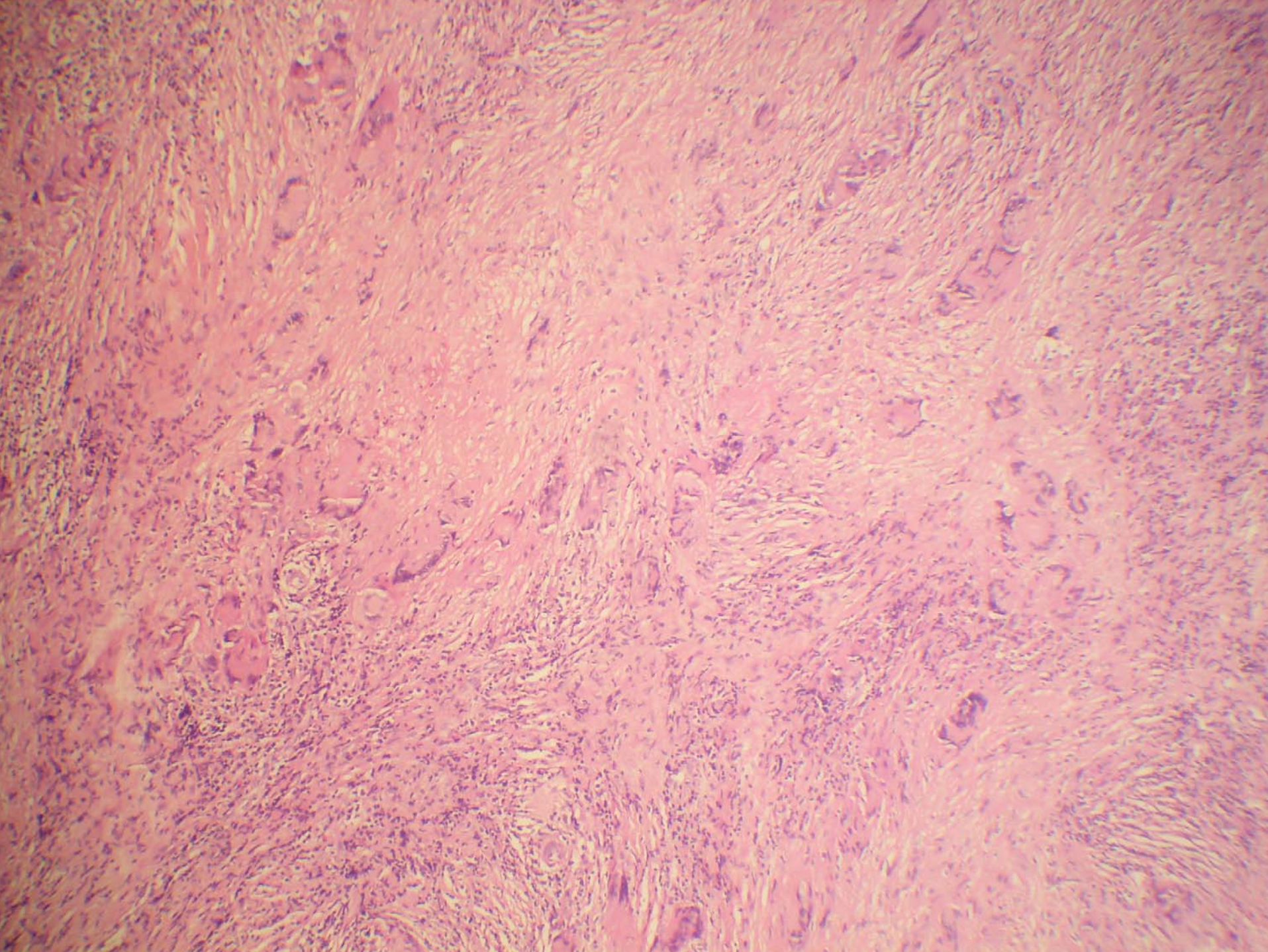
Fungal hyphae

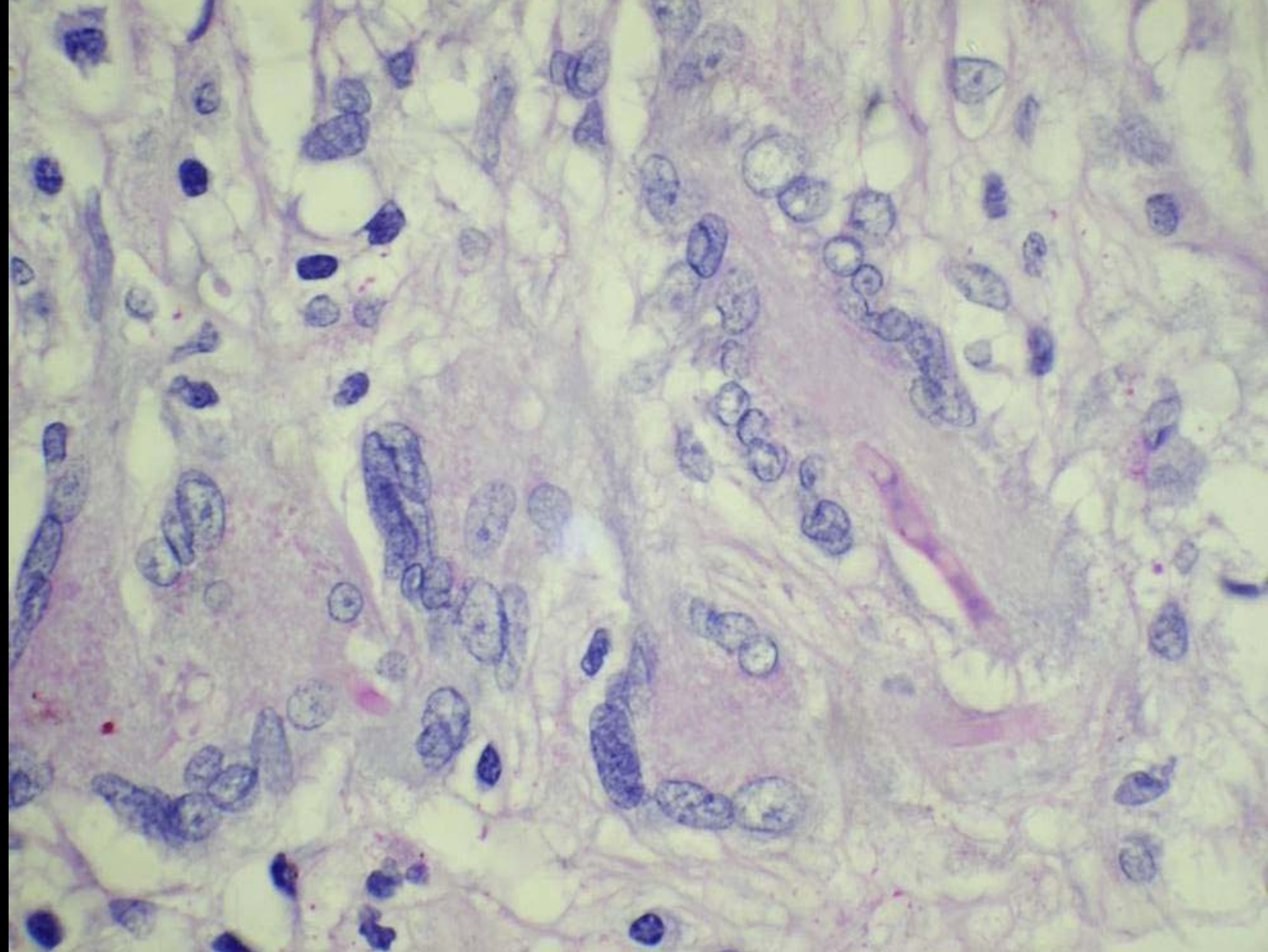


Granulomatous (Chronic invasive)

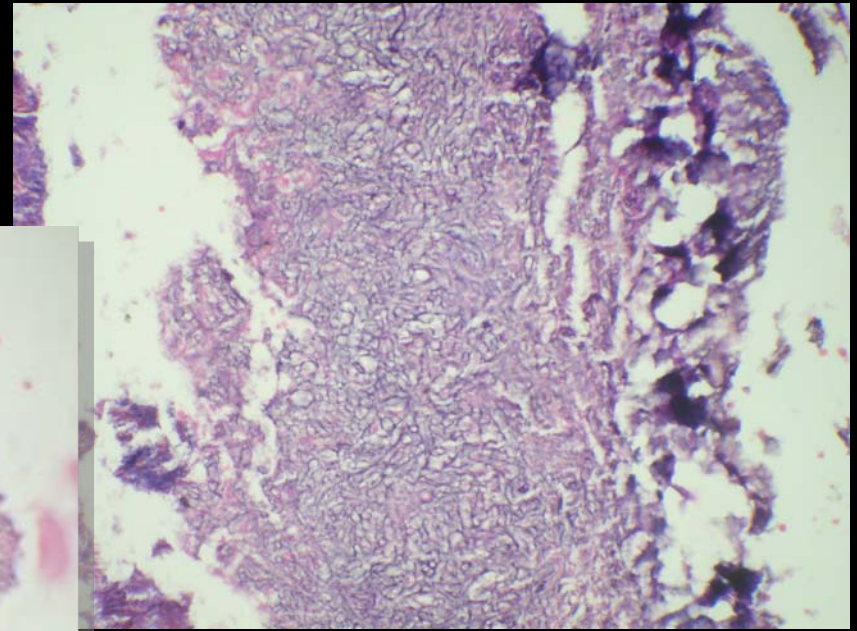
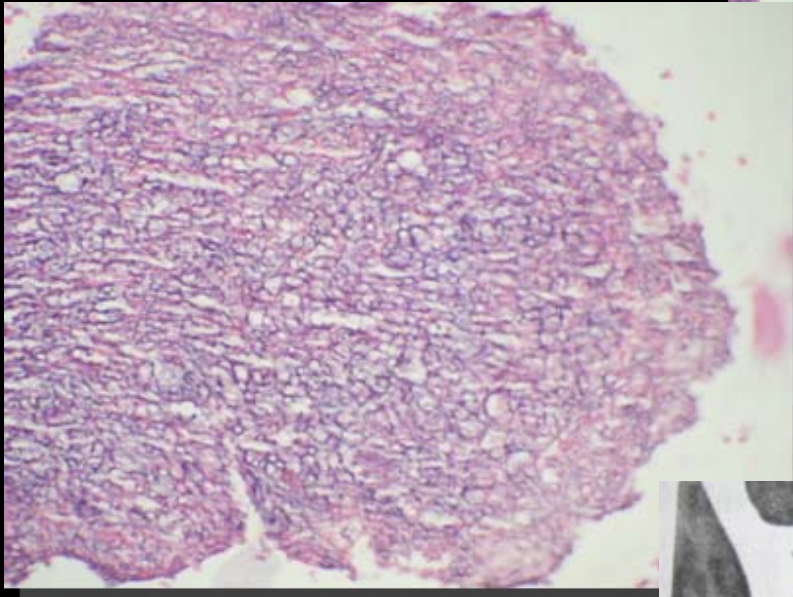
Granulomas with few fungal hyphae
chronic inflammatory infiltrate







Fungal ball



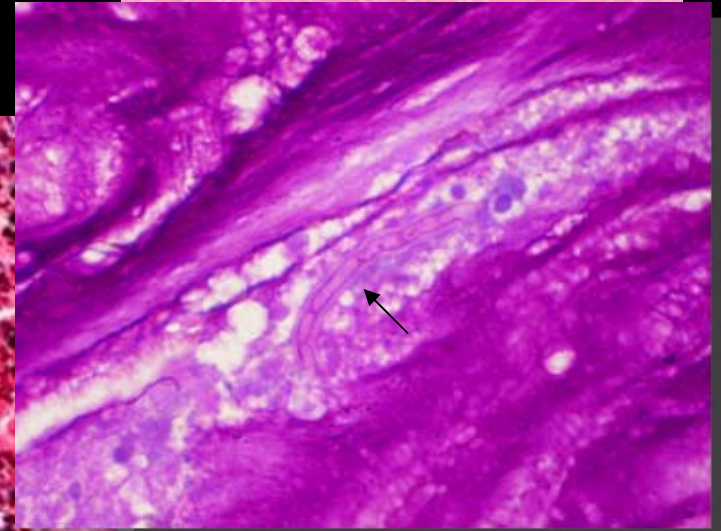
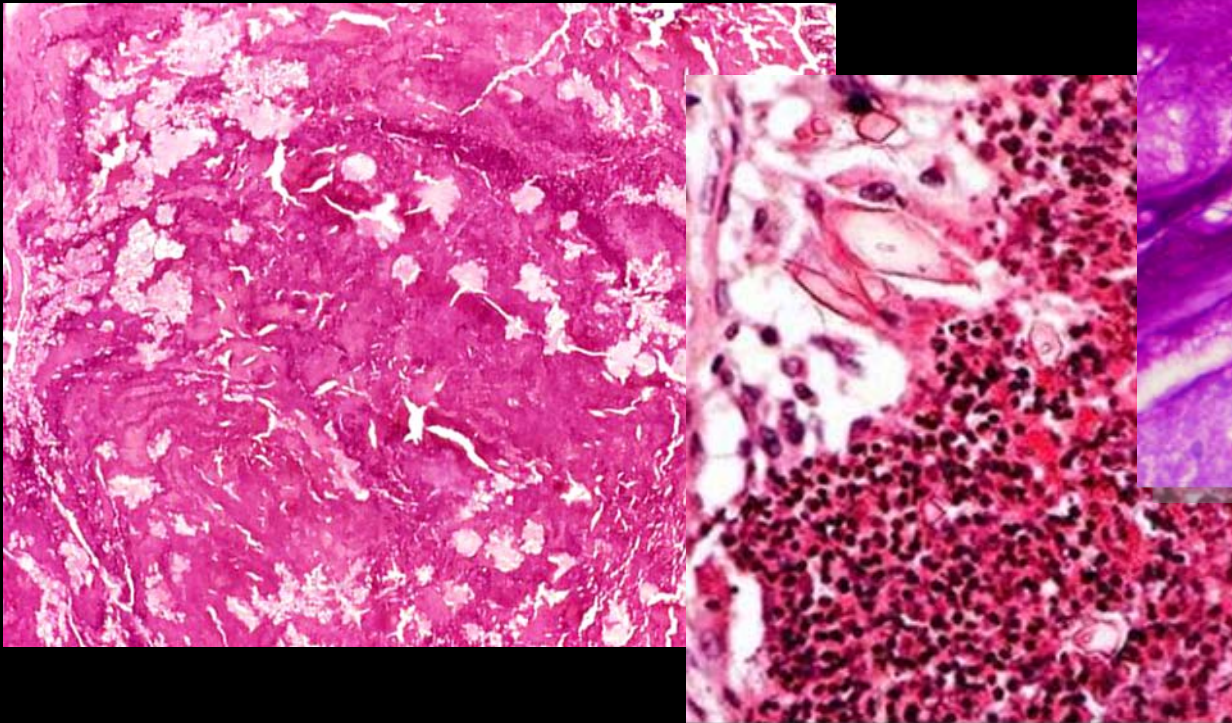
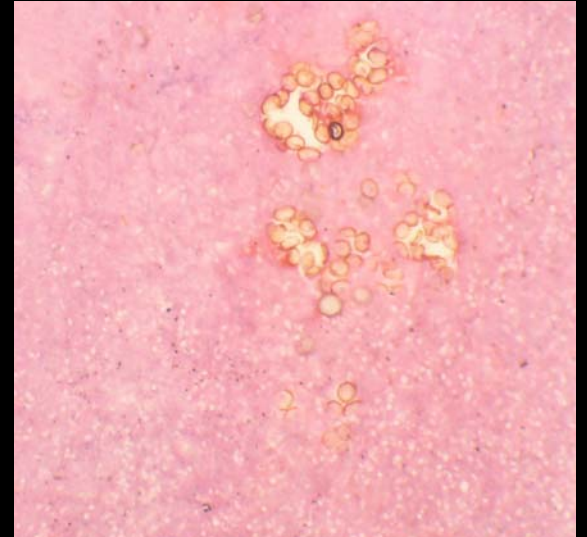
- Usually unilateral
- Involves the maxillary sinus
- Well defined, high attenuation mass
- Occasional flocculent Ca
- Reactive sclerosis of sinus wall



Allergic fungal rhinosinusitis

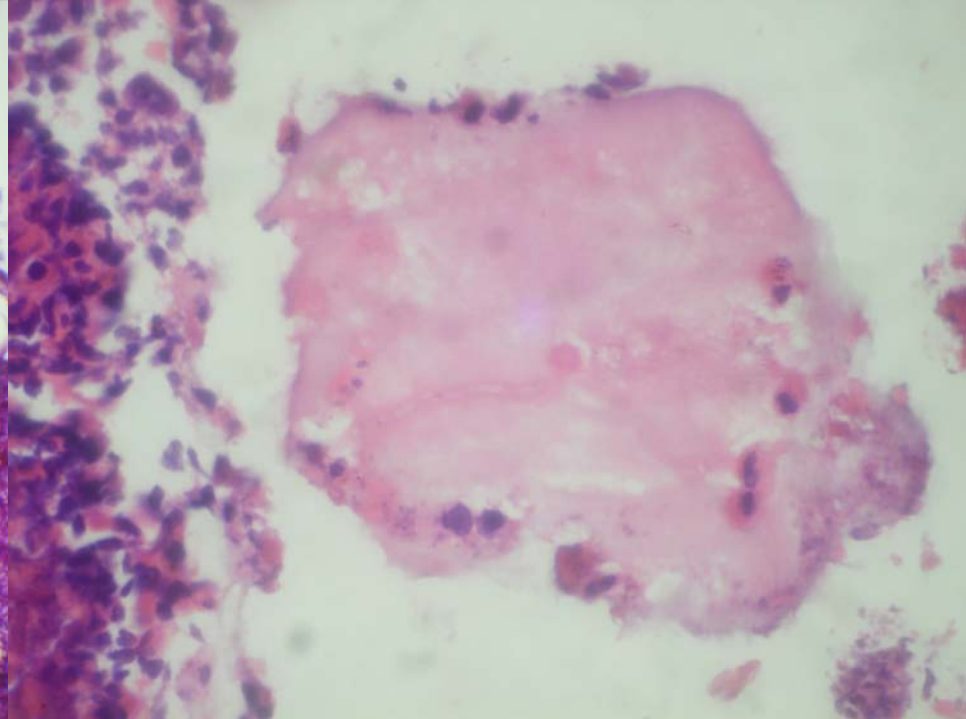
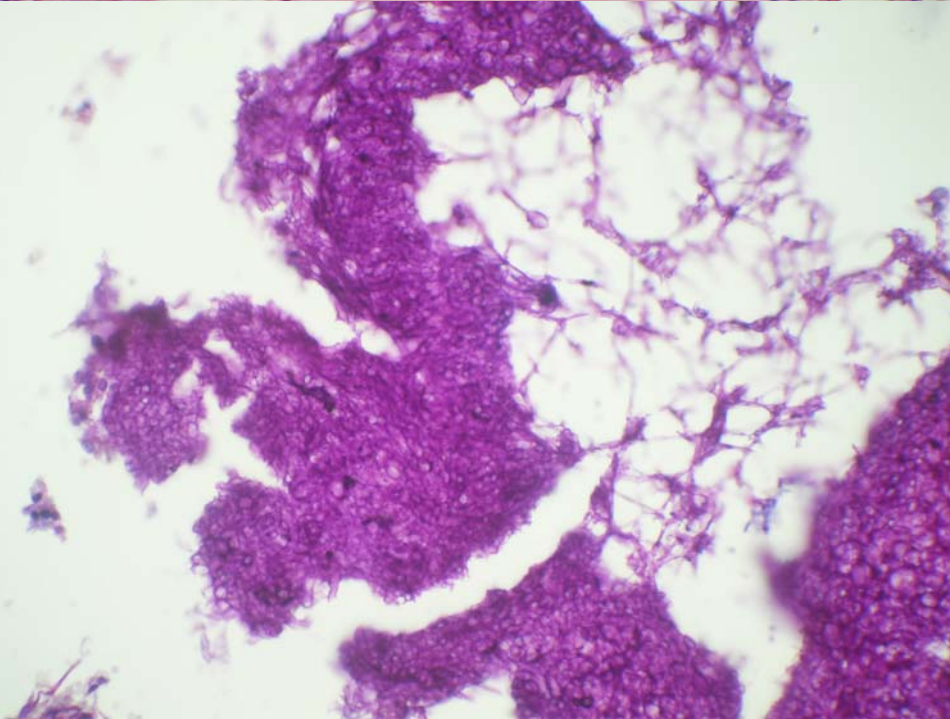
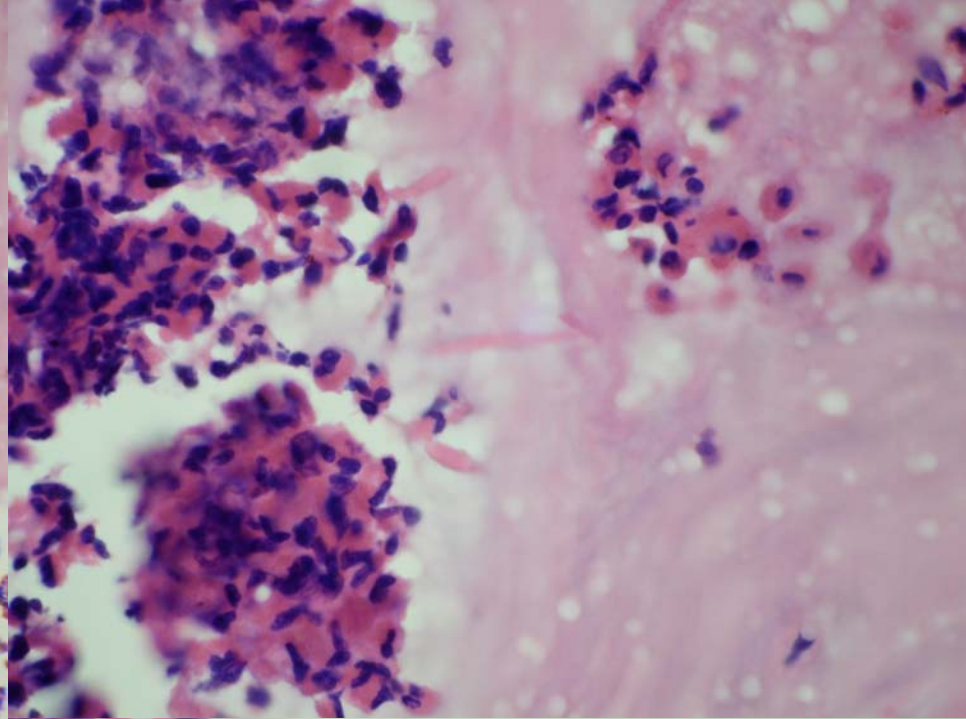
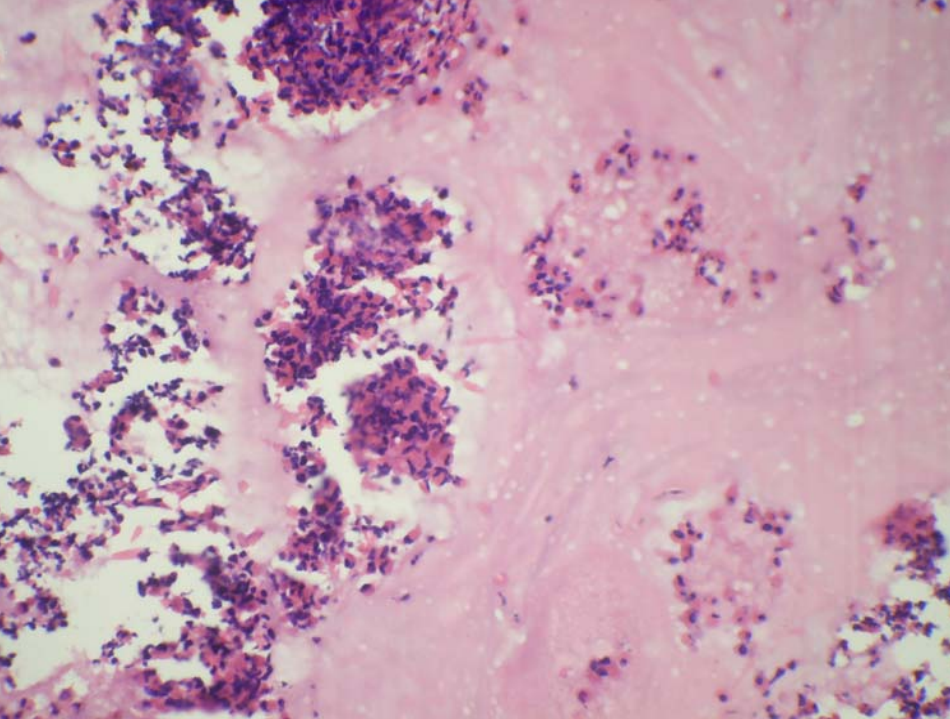
- Type I hypersensitivity
- Nasal polyposis
- Characteristic CT findings
- Allergic mucin without mucosal invasion
- Positive fungal culture of sinus content

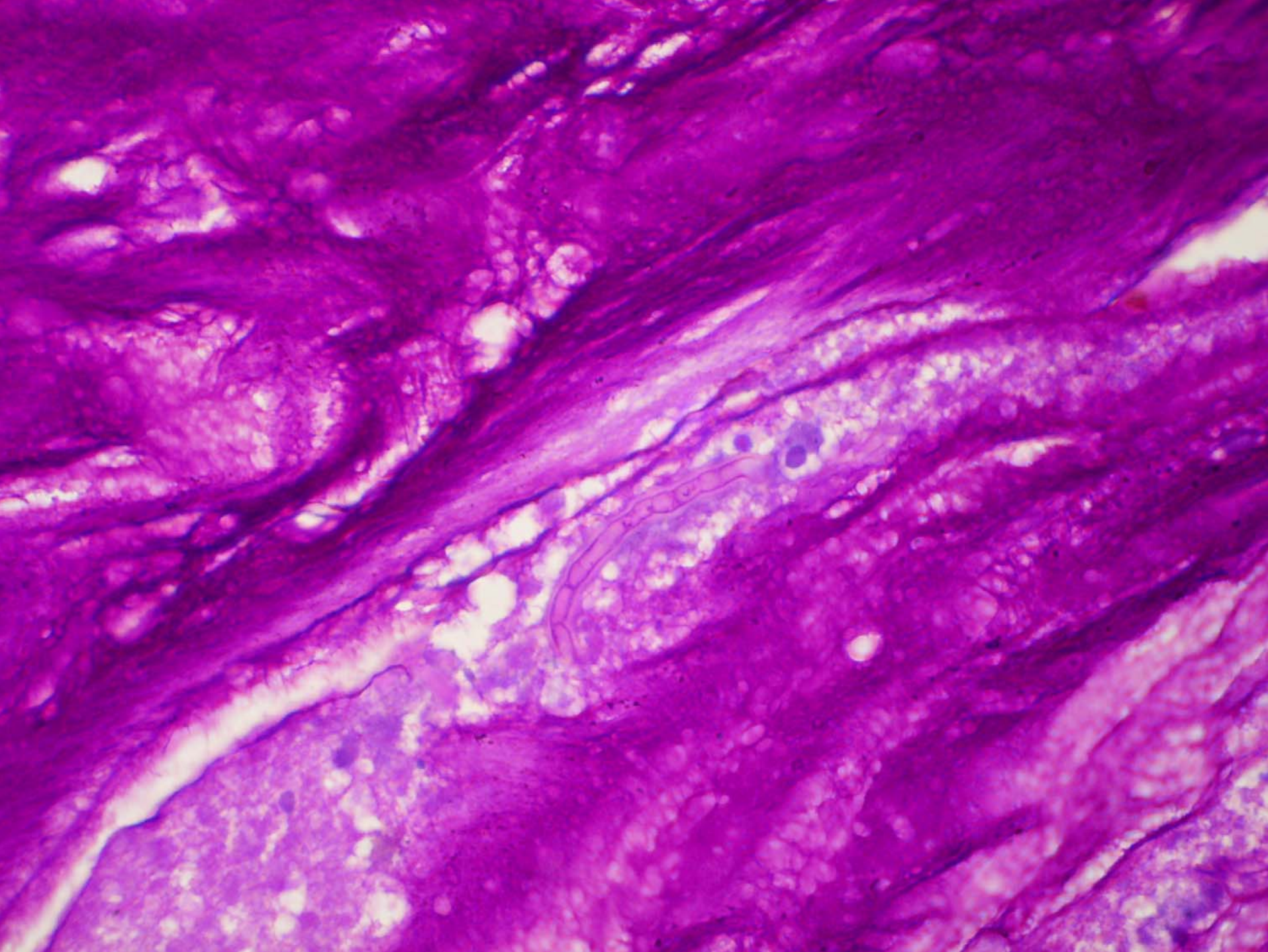
Bent & Kuhn, Otolaryngol Head Neck Surg, 1994

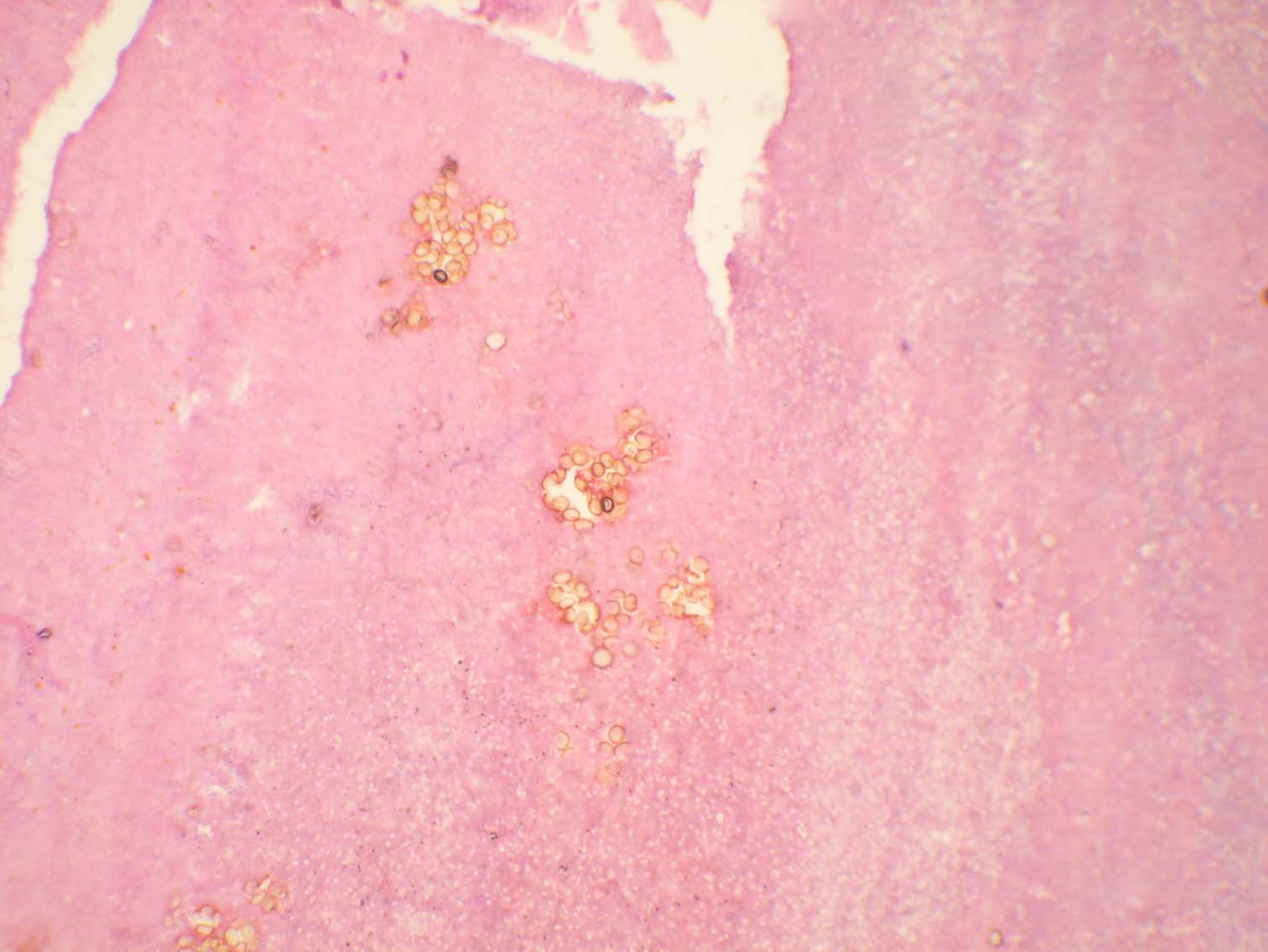


Allergic mucin

- Composed of green, brown, or black mucin displaying the consistency of clay with a gray brown laminated cut surface
- Ranges from a scanty amount to a large volume
- Contained eosinophils, formed tight clusters & imparting a laminated, scalloped-edge shape
- Degenerative changes of eosinophils in the form of smudged, elongated nuclei and collection of small basophilic nuclear debris, presence of Charcot-Leyden crystals







Need to resolve the controversies

- Epidemiology
- Patho-physiology
- Optimization of therapy
- Predicting the outcome

Is it fungal sinusitis or rhinosinusitis?

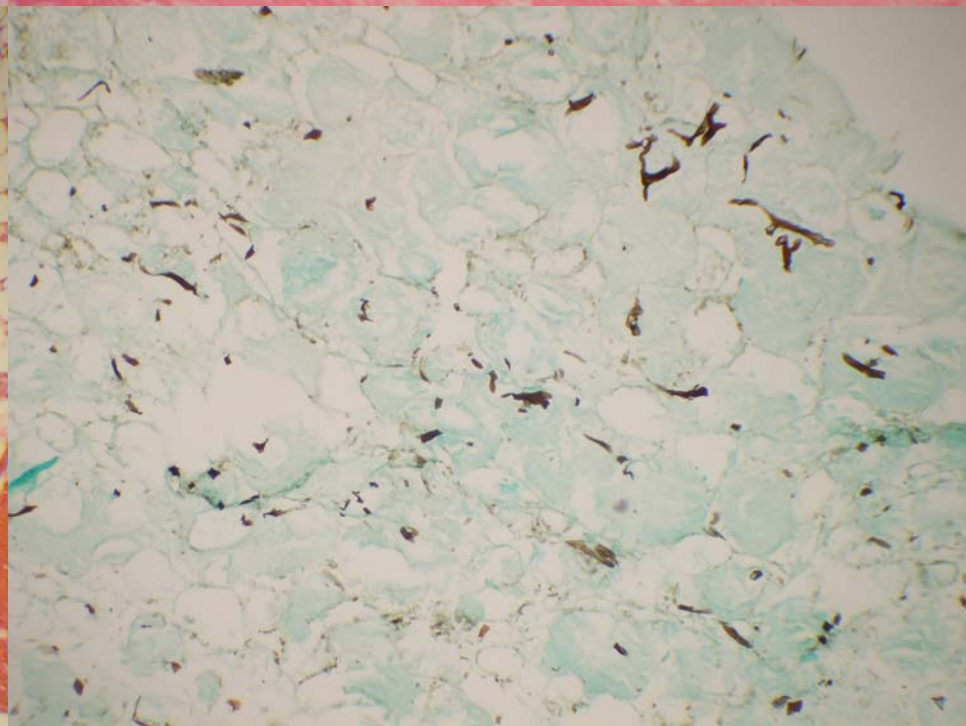
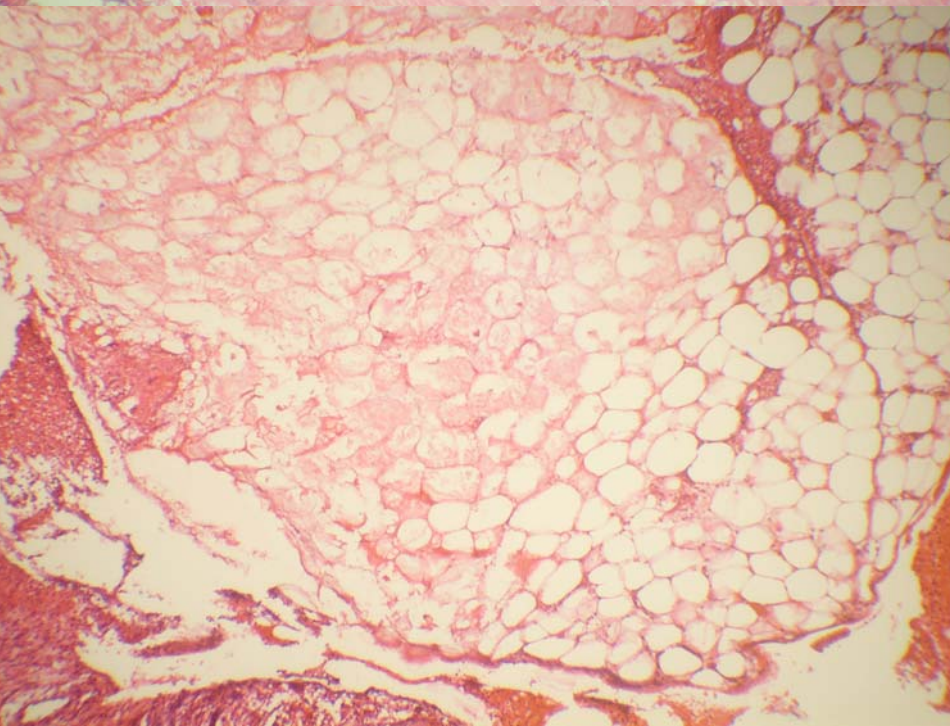
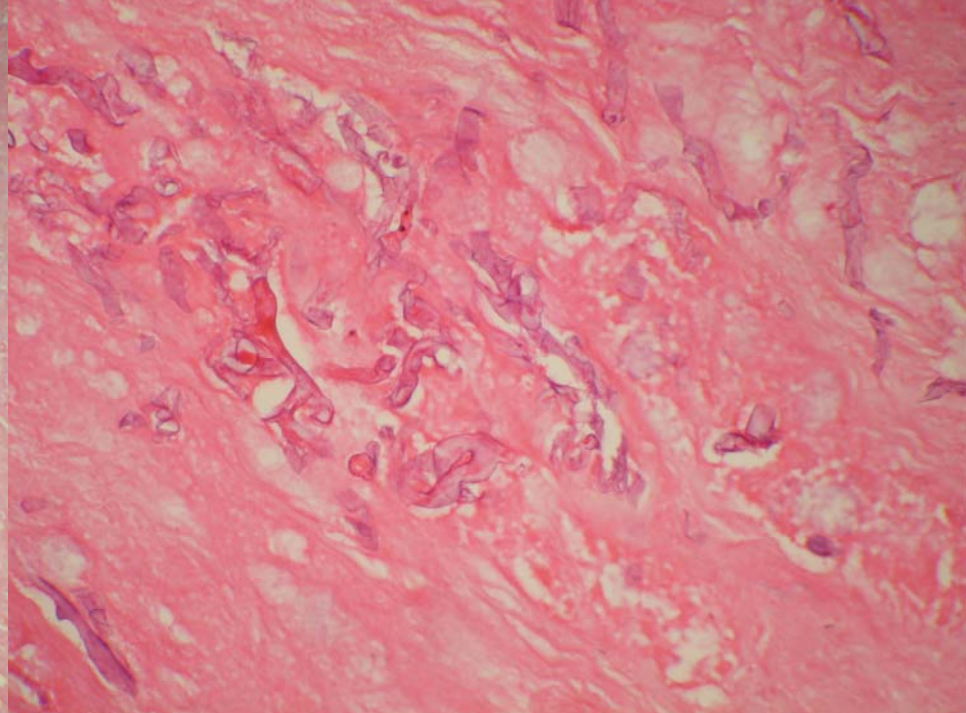
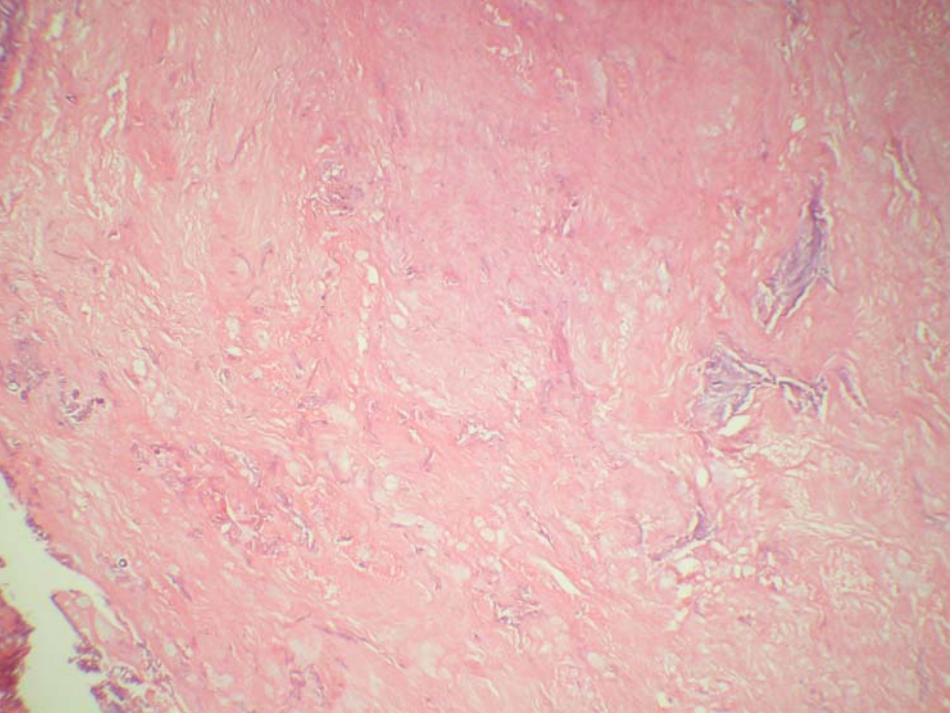
- American Academy of Otolaryngology Head & Neck surgery & their related societies
 - Consensus opinion is to call it rhinosinusitis
 - Fungal sinusitis is almost accompanied by concurrent nasal airway inflammation
 - Many cases preceded by rhinitis
- However, fungal ball rarely cause pathology of nose
- Still, the term rhinosinusitis seems more appropriate

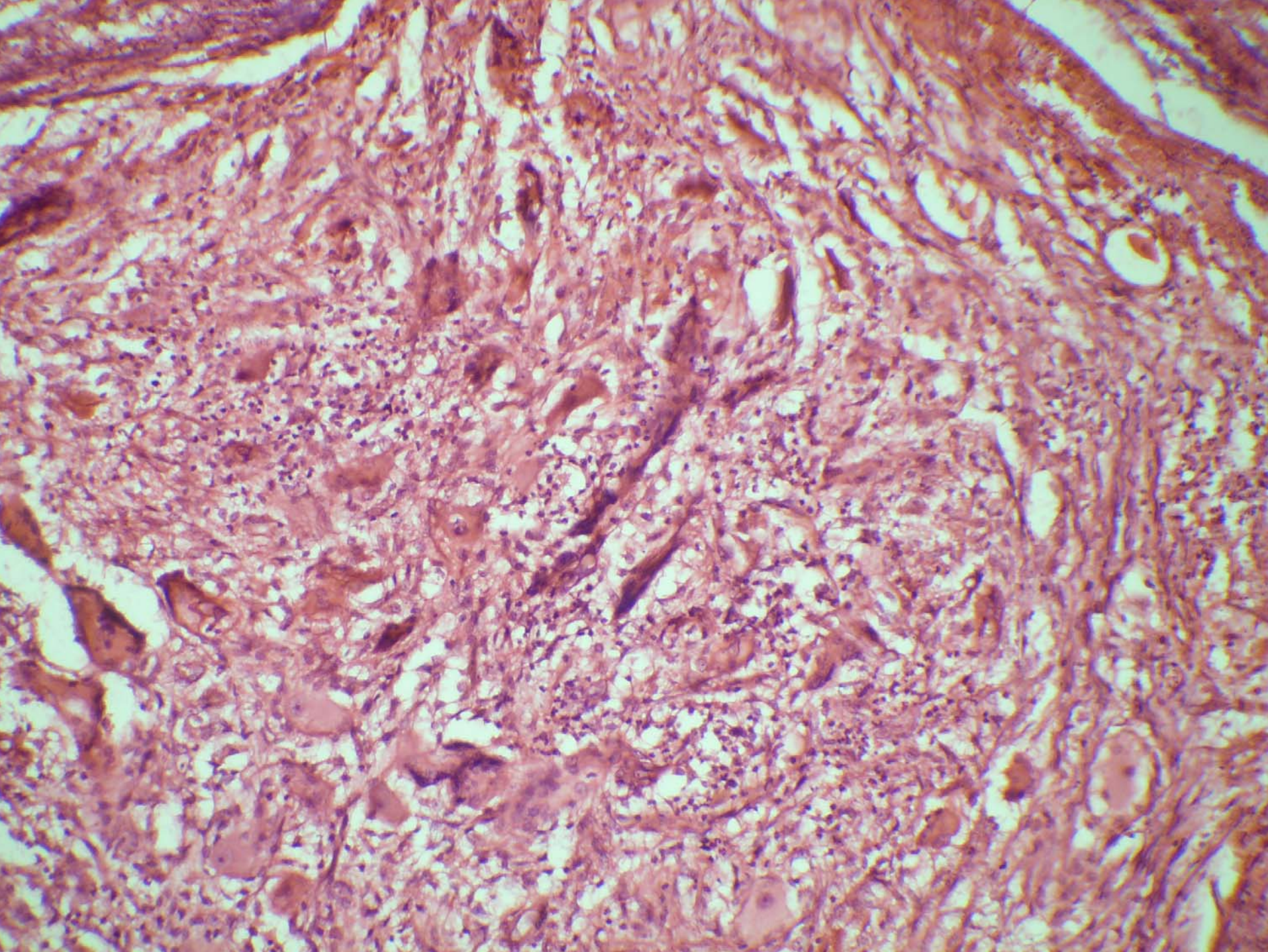
Is it acute invasive or fulminant or necrotizing FRS?

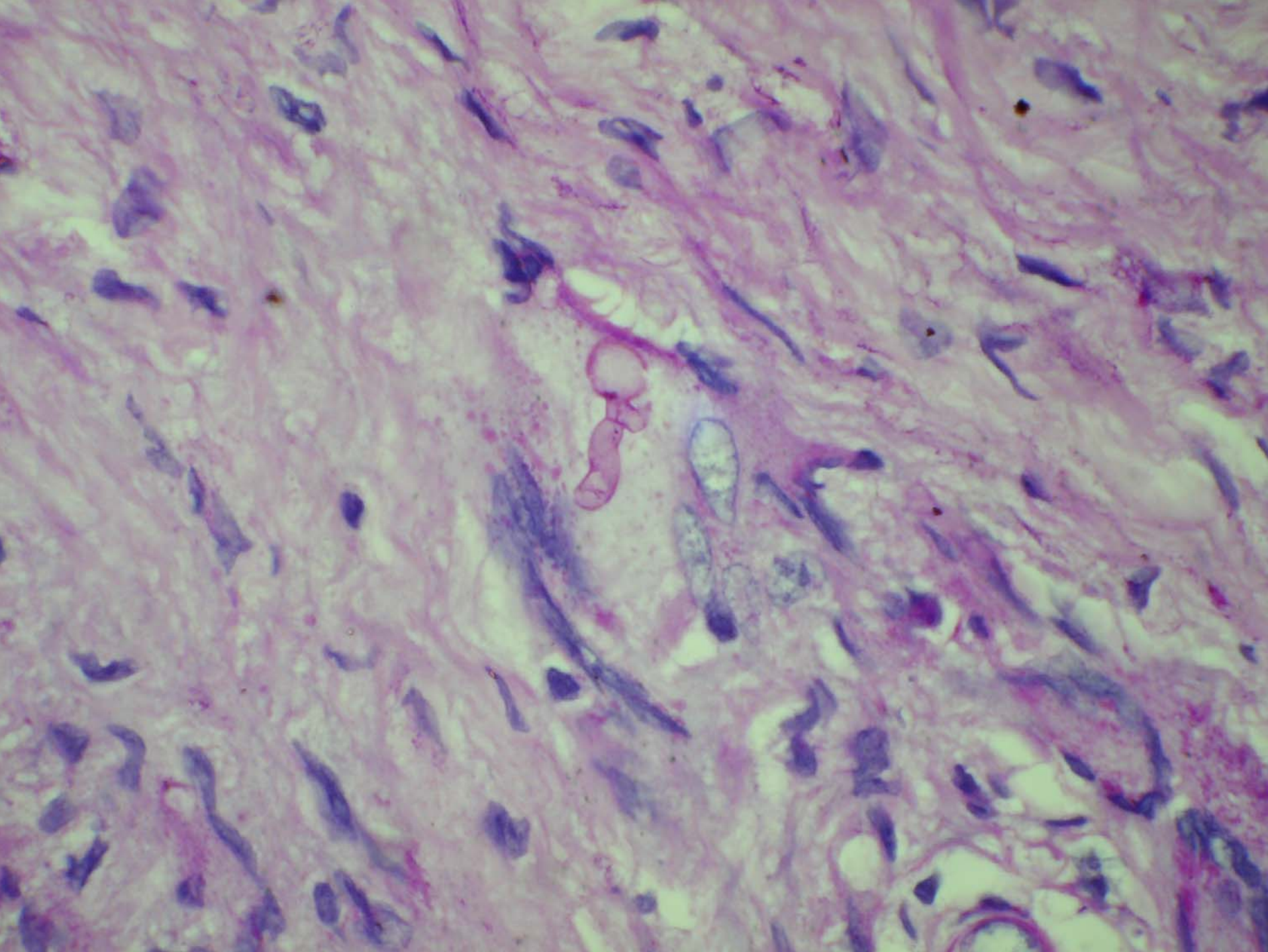
- The term 'fulminant' conveys rapid destruction & often fatal outcome
 - occurs when patients are untreated or severely immunocompromised
 - however, when treated promptly, may take a protracted course
- 'Necrotizing' – in few patients necrotizing reactions with minimal acute inflammatory pathology
- It would be prudent to call it 'Acute Invasive FRS' to describe the disease in immunocompromised host with time course <4 weeks & predominant vascular invasion

Problem in distinguishing acute vs. chronic invasive FRS

- The distinction is imposed by duration of the disease <4 or >4 weeks
- Though acute invasive FRS patients are more immunocompromised than chronic invasive group and vascular pathology is prominent, the difference in relative
- Immunocompromised hosts with acute invasive FRS under treatment may take a protracted course & may fit into chronic invasive FRS
- However, immune status of host & presence of vascular invasion predict the aggressiveness of invasive disease
- Still, this distinction requires further clarification







Are granulomatous & chronic invasive separate entities?

Characters

granulomatous

chronic invasive

Host	immunocompetent	diabetes mellitus
Location	India, Sudan	no specific area
Presentation	proptosis	orbital-apex syndrome
Pathology	granuloma with giant cell, few fungi	necrosis of mucosa, submucosa plenty of hyphae
Mucosal invasion	yes	yes
Fungi	<i>A. flavus</i>	<i>A. fumigatus</i>

Granulomatous vs. chronic invasive

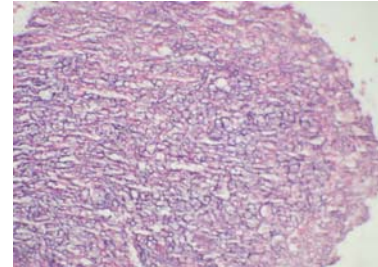
- Both have a chronic course and predominant orbital involvement
- Difference in species of *Aspergillus* may signify geographical distribution of fungi
- Difference in histopathology may represent host immune status & amount of exposure
- No difference in prognosis & therapy predicted
- Diabetics, especially, uncontrolled are susceptible to zygomycetes & that leads to acute invasive FRS
- Thus, emphasizes the need of further clarification

Is it fungal ball or mycetoma or aspergilloma or saprophytic infestation?

- Saprophytic infestation – visible colonization of mucosal crusts of nose without any symptom detected on endoscopic examination (Ferguson, 2000)
 - more frequent after endoscopic surgery
 - ? early form of fungal ball
 - distinguish from the condition of detection of fungi by culture without visible growth from healthy host
- Mycetoma – not technically correct term
- Aspergilloma
 - Indolent cases of locally invasive/non-invasive type described in Sudan (Milosev *et al.*, 1969, Veress *et al.*, 1973)
 - Fungal ball is not always due to *Aspergillus* sp.

Fungal ball

- Radiological evidence of sinus opacification with or without calcification
- Mucopurulent cheesy or clay like material
- Dense conglomeration of hyphae separate from mucosa & without any invasion of mucosa
- Non-specific chronic inflammation of mucosa, without predominance of eosinophils or allergic mucin
- **Caution**
 - Fungal ball may become invasive after immunosuppression (Gungor & Adusumilli, 1998)
 - Allergic mucin may be seen along with fungal ball (J Allergy Clin Immunol, 1998)



Controversies surrounding AFRS

- Main debate originated from the work of Ponikau *et al.*, 1999; Braun *et al.*, 2003; Ponikau *et al.*, 2005
 - with sensitive techniques (nasal lavage, PCR) fungi were detected in >95% of CRS
 - detected fungi in nasal mucus, which contained eosinophils & eosinophil degraded product – Eosinophilic mucin
 - only 42% had type I hypersensitivity & 30% had ↑specific IgE
 - however, the sensitive method detected fungi in the nose of 100% healthy volunteers
 - termed it as ‘Eosinophilic Fungal Rhinosinusitis’ (EFRS)

Controversies surrounding AFRS

- Subsequently Ponikau *et al.*, 2003 extended their work
 - 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, 2000
 - 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

Controversies surrounding AFRS

- Cautions
 - In certain cases of AFRS fungi are sparse & detection difficult – may lead to diagnose as EMRS
 - Considerable overlap exists between AFRS, EFRS, & EMRS in clinical features, radiological, & immunological parameters, though difference in therapy predicted
 - In a prospective study we found considerable overlap between AFRS & EMRS (Arch Otolaryngol Head Neck Surg, 2006)

AFRS-An attempt to resolve the diagnostic dilemma

Arch Otolaryngol Head and Neck Surgery. 2006;132 :173-178

- Prospective study - 70 patients of CR
- Two entities – AFRS, EMRS (Are they interchangeable?)
- M+ F+ n=36 (AFRS likely)
- M+F- n=12 (EMRS likely).
- M- F+ n=4 (Fungal ball)
- M- F- n=18 (CRS due to other causes)

Allergic fungal Rhinosinusitis (AFRS)

No significant difference-nasal polyposis and eosinophilia

Significant difference

Type I hypersensitivity (<0.05)

Charcot leyden crystals (<0.001)

Bony erosion on CT scan (<0.05)

Heterogeneous opacity with expansion of sinuses ($P<0.05$)

EMRS –Significantly high association with asthma ($P<0.05$).

Allergic fungal Rhinosinusitis (AFRS)

Diagnostic predictors of AFRS.

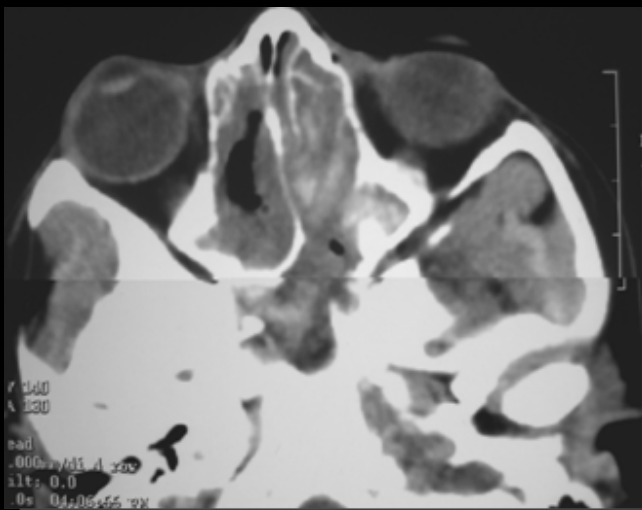
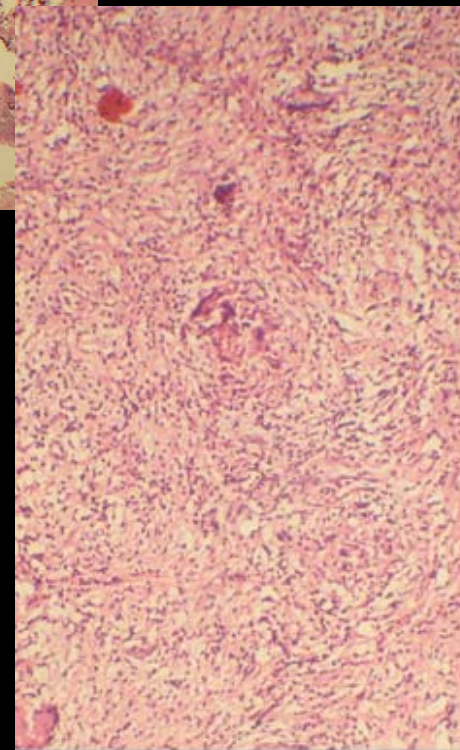
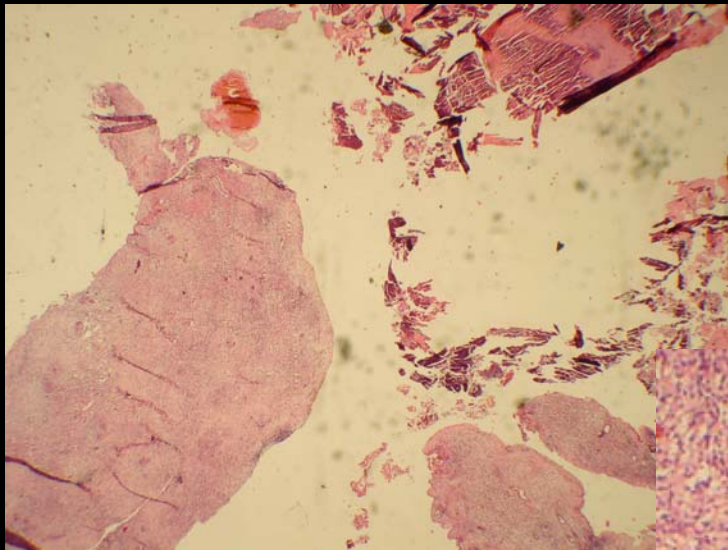
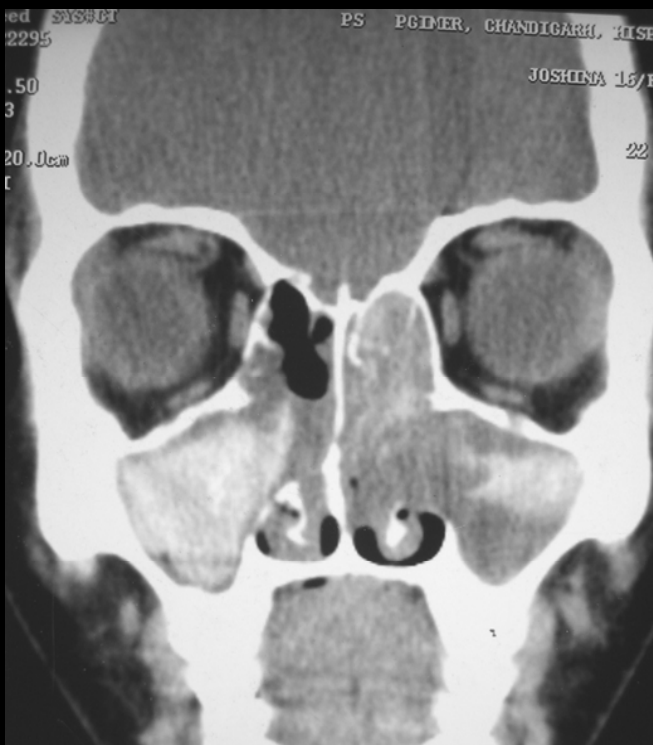
- Fungal elements and allergic mucin in the sinus content
- Type I hypersensitivity*
- Charcot Leyden crystals
- Bony erosion *
- Heterogeneous opacity and sinus expansion in CT*

*Preoperative Predictors

Is fungus a bystander?

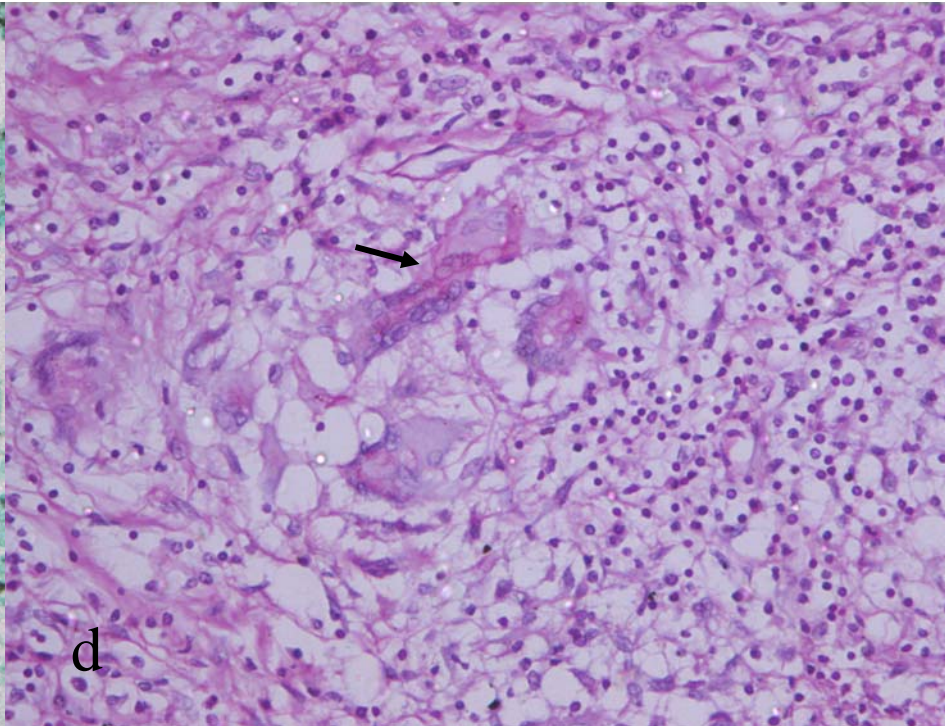
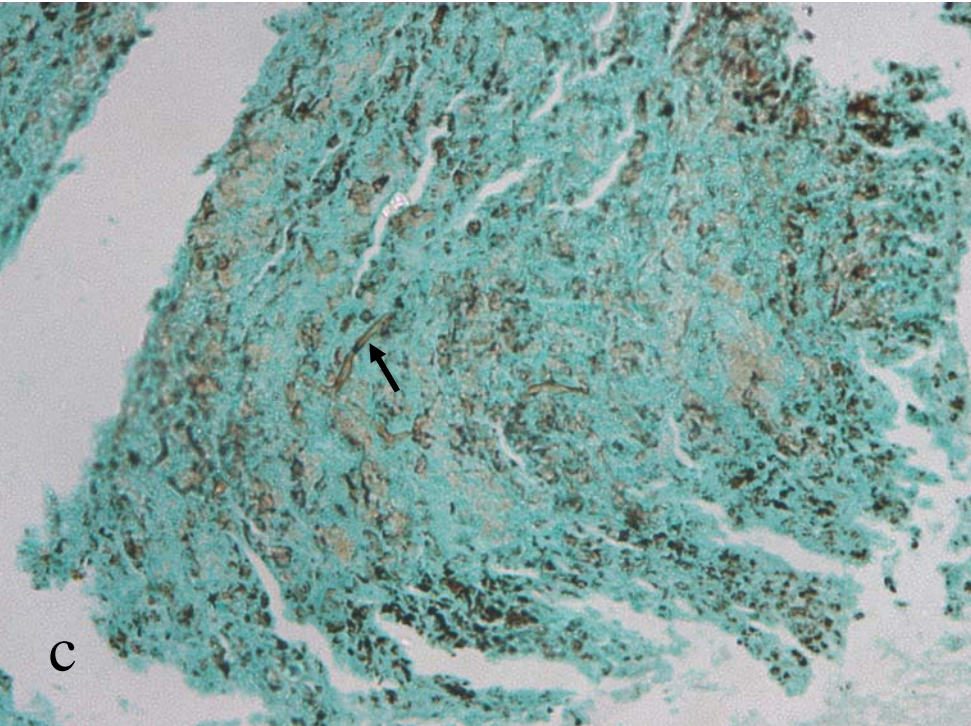
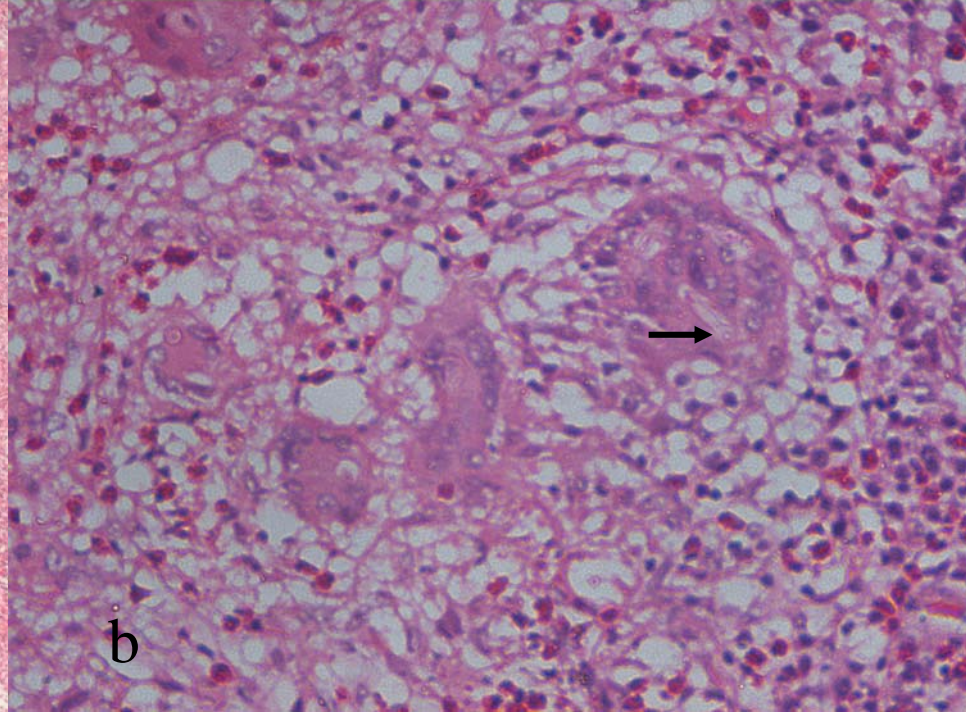
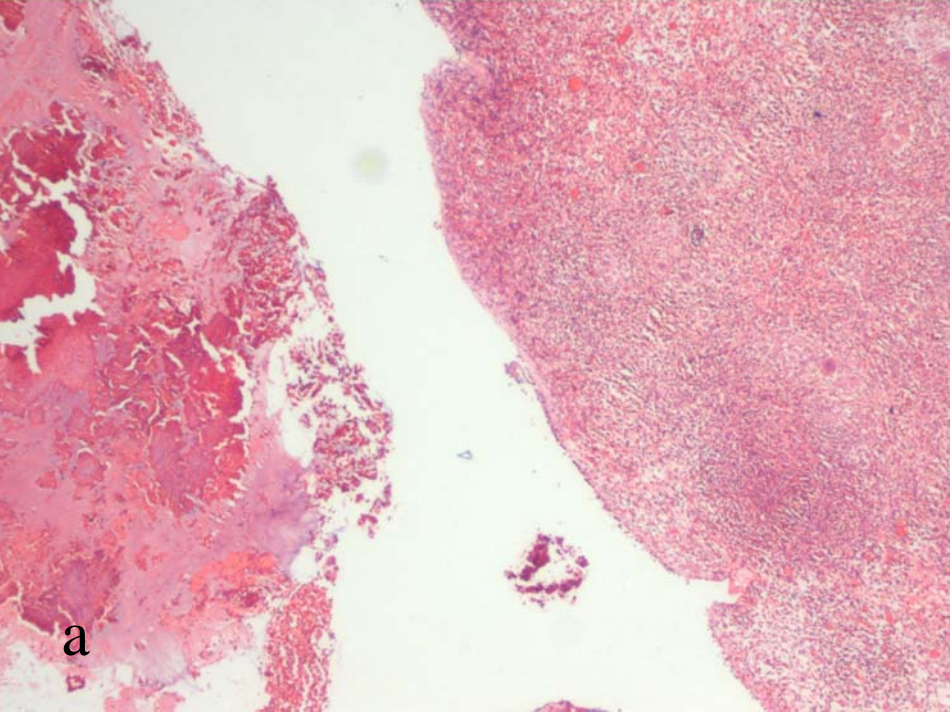
- In AFRS, it is proposed that fungi produce Ag that stimulates IgE, IgG, & IgA production
- It is known that in AFRS (like ABPA) – a Th2 mediated eosinophilic reaction
- Once initiated, Ag independent permanent phase (Clin Rev Allergy Immunol, 2006)
- But what triggers its pathway?
 - role of allergen, fungus derived Ag, bacteria, bacterial super antigens are proposed
 - specific IgE to Staphylococcal enterotoxin present in 60% nasal polyp & 80% nasal polyp with asthma (J Allergy Clin Immunol, 2001)
- To prove the role of fungi the requirements are:
 - definite evidence of T cells in sinus responds to fungal Ag
 - removal of fungal Ag ameliorates the disease

Allergic fungal rhinosinusitis ? invasive



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

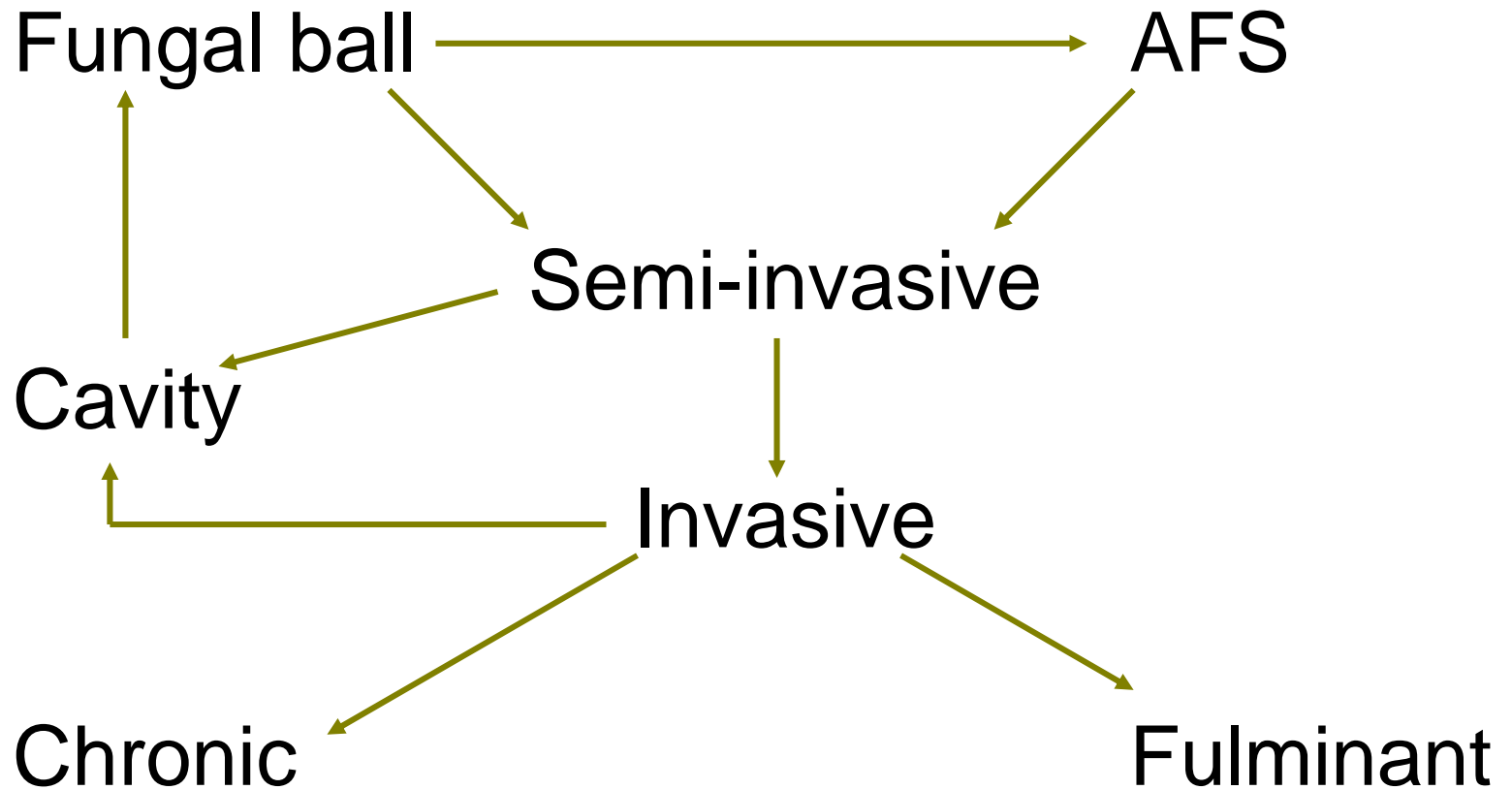
- In 2004, 6 (21%) cases of mixed reaction (New Delhi experience)



Is there another type of chronic destructive, non-invasive FRS?

- Proposed by Rowe-Jone & Moore-Gillon, 1994
- Characterized by
 - Sinus expansion, bony erosion, without tissue invasion
 - Chronic inflammation, intermediate between allergic & chronic invasive
 - No proptosis/facial mass
 - More violent than fungal ball presentation
 - Though long & chronic course like AFRS, pathology & immune status are different
- It may a variant of non-invasive type that destroys sinus wall by pressure (Robb, 1986)

Can it be a progressive spectrum of a disease?



Study required

- Requirement of separation of granulomatous & chronic invasive types
- Is there any subtype of granulomatous invasive – chronic eosinophilic lymphocytic granuloma exists?
- The difference between acute & chronic invasive?
- Does chronic destructive, non-invasive type exists?
- Correct definition of AFRS
- What about EFRS, EMRS?
- Does AFRS type lead to invasive type?
- Is fungi bystander in whole process?
- Whether these types are a spectrum of single disease?

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
- holding an international workshop at the Chandigarh, India during 9th – 11th February 2008

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Chandigarh

