TIMM
Trends in Medical Mycology

Allergic and chronic aspergillosis: lessons for the busy mycologist:

Sinusitis

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Fungal rhinosinusitis: different syndromes!!

- Chronic rhinosinusitis is the most common chronic disease affecting 20% of the population (in the US affecting **37 millions**). *Vital Health Stat 1995, 10:89*
- Noninvasive and noninvasive (Hora, 1965)
- A fulminant form with rapid course (McGill, 1980)
- Description of nasal polyposis, crust formation, sinus cultures (+) for *Aspergillus* sp, similar to ABPA (Safirstein, 1976)

Can it be a progressive spectrum of a disease?

- Saprophytic
- Fungal ball
- semi-invasive
- invasive
- Chronic
- acute

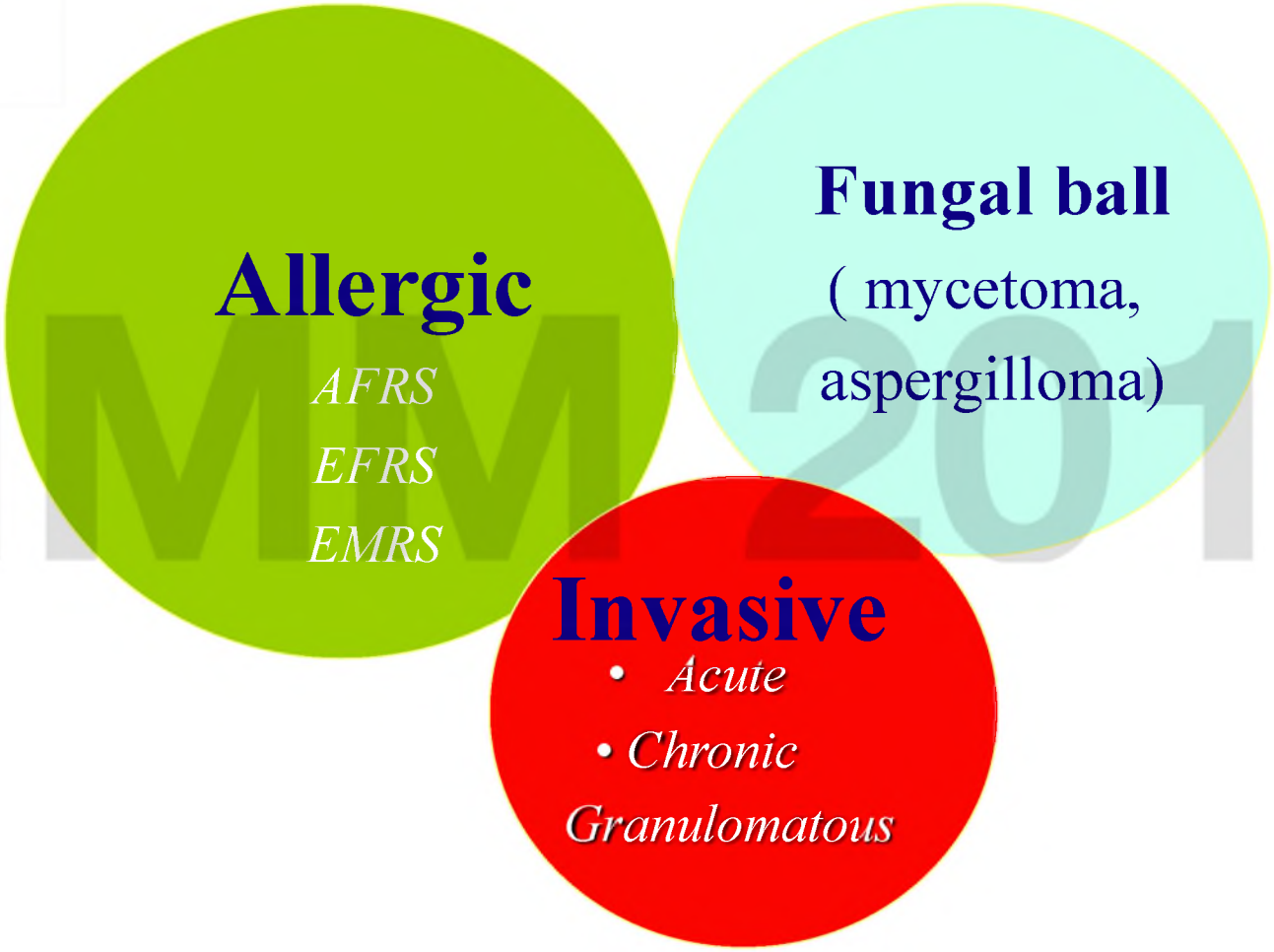
AFRS

EFRS

EMRS

Rowe Jones & Moore Gillon, 1994

What are the clinical forms?



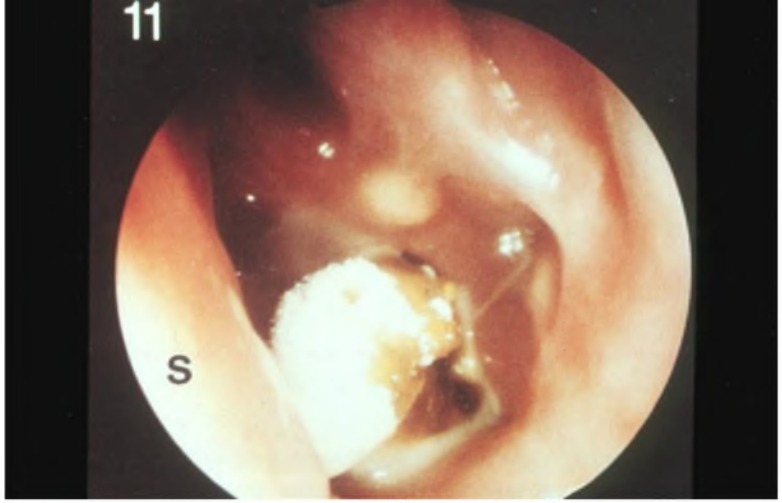
DeShazo. Arch Otolaryngo Head Nech Surg 1997; 123:1181

type	Clinical clues	Most common causes	Diagnosis	Initial management
Noninvasive fungal sinusitis	**Immunocompetent** Intractable symptoms Allergic rhinitis, asthma Nasal polyps Calcifications (CT) **Proptosis** (children)	Hyaline molds Aspergillus sp Fusarium sp Dematiaceous molds Bipolaris sp Curvularia lunata Pseudallescheria boydii	**Aspiration** of sinus contents **Silver-impregnation stain and culture of aspirate** **Peanut butter or cottage cheese content** **Biopsy of healthy and diseases mucosa to rule out tissue invasion**	surgery
Invasive fungal sinusitis	**Immunocompromise** Calcification (CT) **Orbital apex syndrome** Proptosis (adults)	Hyaline molds Zygomycetes Rhizopus oryzae Aspergillus sp Fusarium sp Dematiaceous molds P. boydii	**Early endoscopic** evaluation **Biopsy** (mucosa and bone) Silver-impregnation stain **open biopsy if endoscopy negative**	**Emergency surgery** AmphoB Reversion of immunosuppression

Saprophytic Aspergillus sinusitis

- Simple colonization of nasal and paranasal sinus without any symptoms
- Over mucous crusts in patients with a previous sinus surgery
- Further extension may lead to fungal ball formation

www.aspergillus.man.ac.uk



Is it fungal ball or saprophytic infestation?

- Saprophytic infestation –visible colonization of mucosal crusts of nose without any symptom detected on endoscopic examination (Ferguson, 2000)

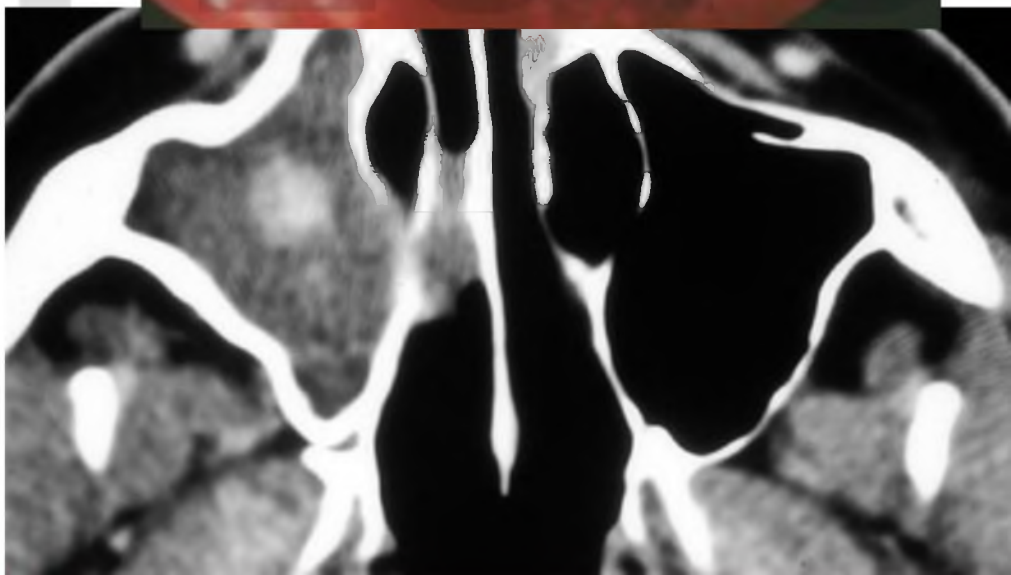
✓ more frequent after endoscopic surgery

✓ ? early form of fungal ball

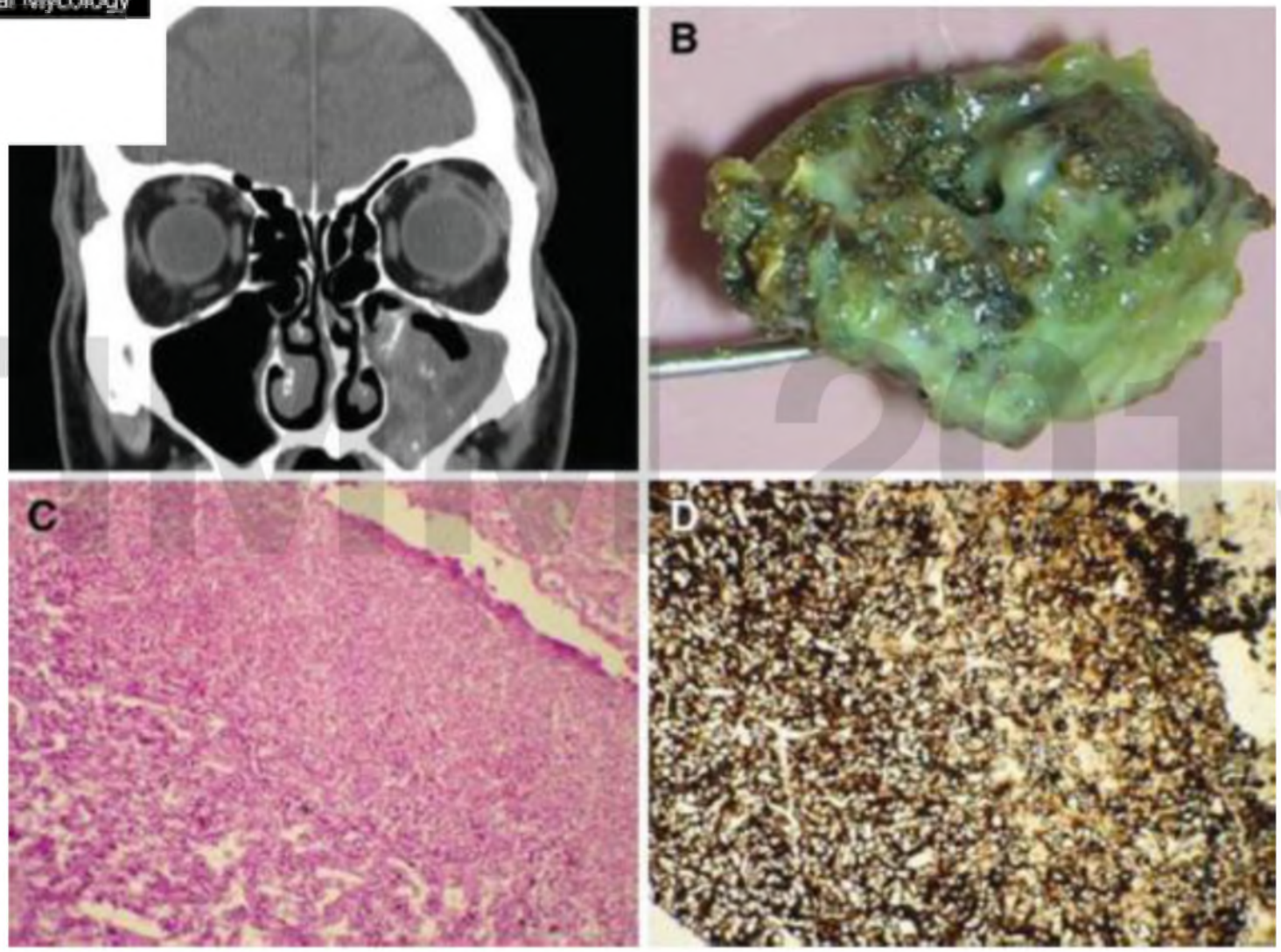
- distinguish from the condition of detection of fungi by culture without visible growth from healthy host
- –Indolent cases of locally invasive/non-invasive type described in Sudan (Milosev *et al.*, 1969, Veress *et al.*, 1973)

Fungus ball

- Mucopurulent cheesy or clay like material
- Dense conglomeration of hyphae separate from mucosa & without any invasion
- Non-specific chronic inflammation of mucosa, without predominance of eosinophils or allergic mucin
- opacification
- Bony sclerosis, no erosion



Fungus ball in the left maxillary sinus



Chakrabarti A, et al. Laryngoscope 2009;119(9): 1809-18

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Allergic Fungal Sinusitis (AFS)

Allergic fungal rhinosinusitis: How common?

- Incidence of AFRS in chronic rhinosinusitis is **7%**. *(Cody DT. Laryngoscope.1996; 4:169)*
- In a recent prospective cohort from the US, fungi were isolated from **94%** of patients with chronic rhinosinusitis. *(Ponikau JU. Mayo Clin Proc.1999; 74:877)*
- In a recent study from Austria, fungi were isolated from 91.3% from patients with chronic rhinosinusitis. **75.5%** of patients had fungal elements on histopathology. *(Braun H. Laryngoscope.2003; 113:264)*

Allergic Fungal Rhinosinusitis (AFRS)

- Most common form of fungal sinusitis
- Controversy: infectious vs allergic?
- A recently recognized entity

  1976: First described in patients with Allergic broncho-pulmonary aspergillosis *(Safirstein. Chest 70: 788)*

  1983: Few cases with the histologic triad of necrotic eosinophils, charcot-Leyden crystals and non-invasive fungal hyphae and was named *Allergic Aspergillus sinusitis* *(Katzenstein. J Allergy Clin Immunol 72:89)*

AFRS

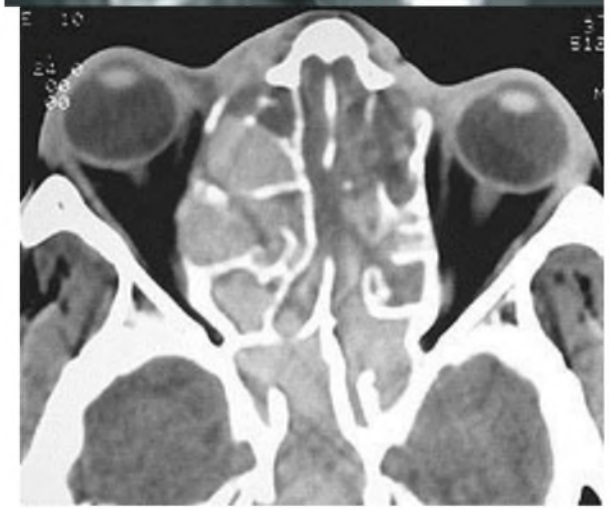
- "hypertrophic/hyperplastic sinus disease or HSD", or "chronic rhinosinusitis or CRS"). hypersensitivity
- 80% diffuse polyps
- Aspergillus precipitins +ve in 85%
- Sinus CT hyperattenuation.
- •Can be bi-or unilateral.
- •Can erode through sinus bone margins into orbit or intracranium

- Nasal obstruction, recurrent sinus infections, loss of smell
- Mortality is rare even with extensive disease
- Visual loss is rare

CT in AFRS

- Sinus opacification
- Expansion
- Bony erosion 20%)
- No tissue invasion
- Remodeling common

✓ extension to surrounding structures can happen BUT due to pressure and not invasion



Eosinophilic mucin

- Characteristic "eosinophilic mucin" (a sinus luminal **peanut-buttery** inspissate of massive numbers of pyknotic eosinophils) is seen grossly at surgery and further defined histopathologically.
- Allergic mucin is fungal stain positive for **sparse scattered hyphae; non-tissue-invasive**.
- Surgical sinus fungal culture positive.

Pathophysiology of AFRS

- The pathophysiology of AFRS is not fully understood and is in constant evolution.
- Initial theories favored an immunoglobulin E-mediated immune response to fungal antigens
- Central role of cytokines derived from respiratory epithelial cells, including interleukin IL-25, IL-33, and thymic stromal lymphopoietin, in the orchestration of both innate and adaptive T helper immune responses

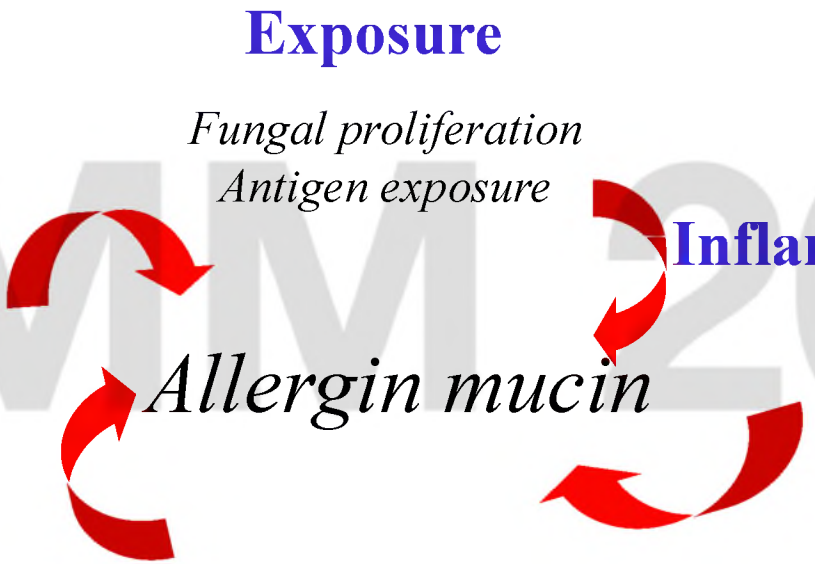
Curr Opin Otoryngol Head Neck Surg 2014 Jun;22(3):221-6

Pathophysiology of AFS

Local Factors
-Mucostasis
-Anatomic anomaly

Enviromental
Fungal exposure

Genetic
-Atopy
-Unknown



Steroids
Immunotherapy

Marple: Laryngoscope 111:1006. 2001

Criteria for Diagnosis of AFS

- No consensus but several proposal share:
  - Presence of allergic mucin on histopathology
  - Presence of non-invasive hyphae on histopathology +/- fungal culture
  - Fungal Ig-E mediated hypersensitivity
  - Nasal polyposis
  - High-signal intensity opacification of sinuses on CT scan
- ? Associated atopy (65%) with asthma (50%)

Marple: Laryngoscope 111:1006. 2001, Bent & Kuhn 1994

Eosinophilic mucin rhinosinusitis (EMRS)

–Eosinophilic mucin present without fungus

–A systemic disease with dysregulation of immunological control

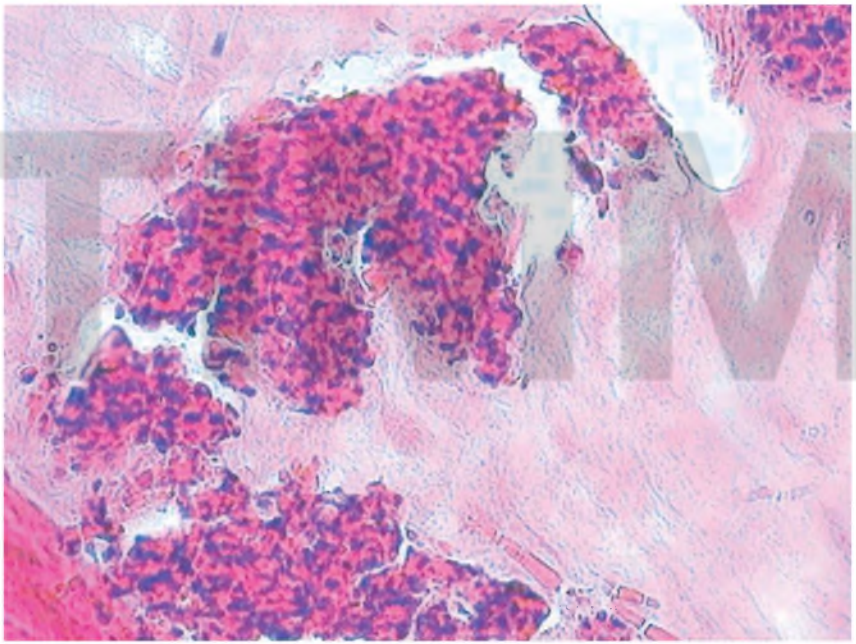
–Significantly associated with asthma, ↑incidence of aspirin sensitivity, ↑incidence of IgG1 deficiency

–Though systemic steroid could be useful, fungal immunotherapy & antifungal agents would be ineffective *Ferguson, 2000*

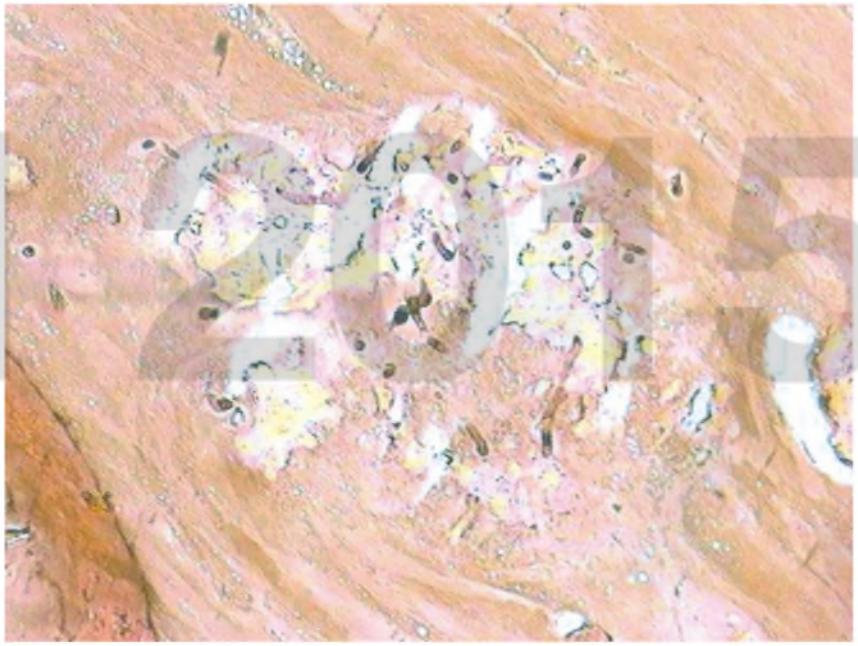
Surgical handling of specimens very crucial.
"More is better"

- All surgical procedures should be performed **without** a power microdebrider or the use of suction devices until sample collection is complete.
- Placing specimens on absorbent material (towels, cotton sheets, gauze): significant reduction of collected mucus.
- Use nonabsorbent material (a saline-moistened sheet of sterile used x-ray film)
- Multiple section from different areas of the nose and paranasal cavities *Braun H, et al. The laryngoscope 2003*

AFRS the importance in staining



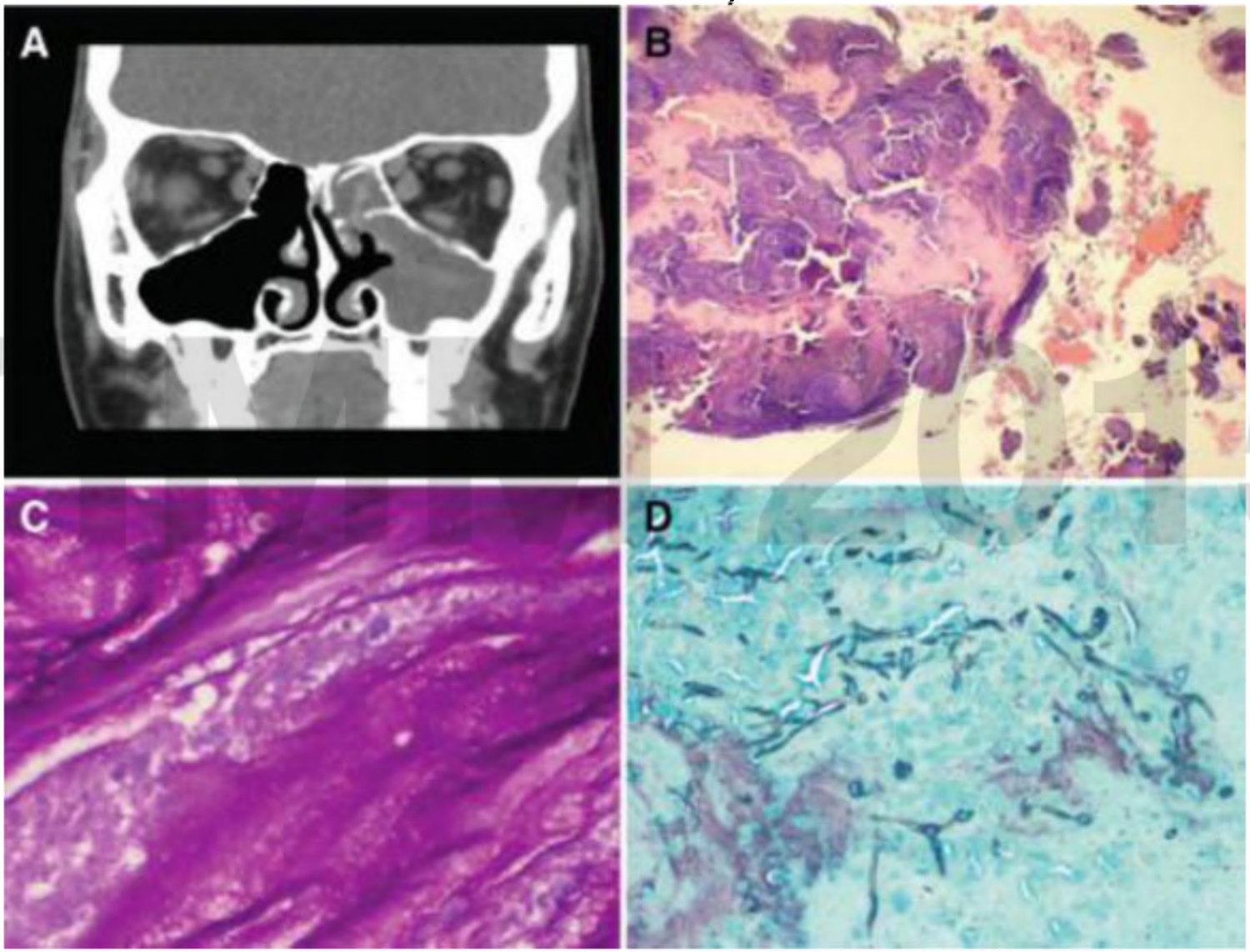
Eosmophilic cluster within the nasal mucus
(H&E stain) x300



AFS Gomori methenamine silver.

Braun H, et al. The laryngoscope 2003

Recurrence of AFRS-right etmoid and maxillary sinus



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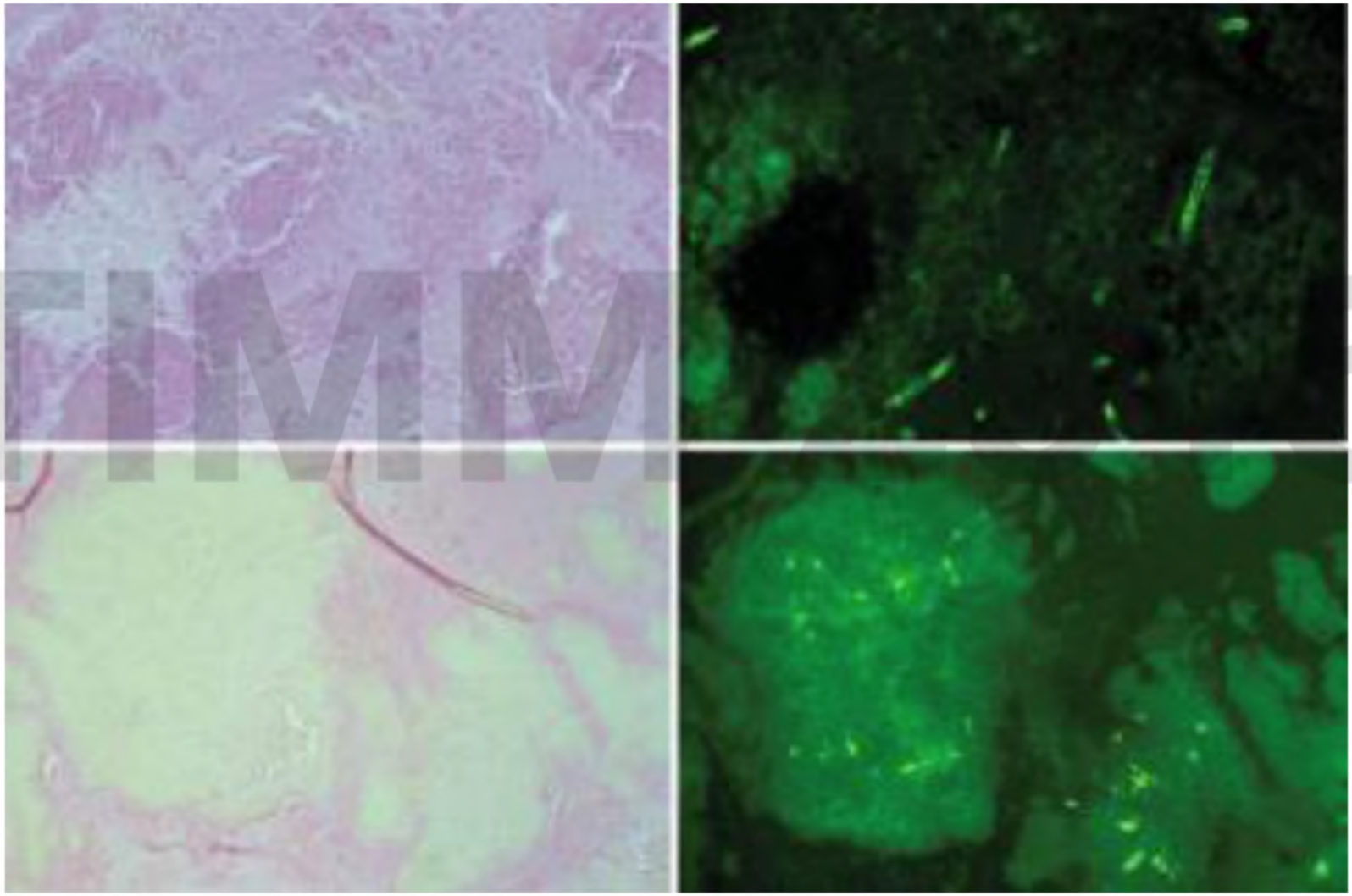
AFRS - alternative ways of visualizing fungi (chitinase stain, polyclonal antibodies)



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AFRS- An attempt to resolve the diagnostic dilemma

Saravanan K, et al, 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). *Saravanan K, et al, Arch Otolaryngol Head and Neck Surgery. 2006;132 :173-178*

Controversies surrounding AFRS

- With sensitive techniques (nasal lavage, PCR) fungi were detected in >95% of CRS
- 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)

Ponikau *et al.*, 1999; Braun *et al.*, 2003; Ponikau *et al.*, 2005

Treatment Goals for AFS

- Clear current episode
- Reduce number of recurrences (90% of cases)
- Improve quality of life
- Patient education about the nature of the disease

Steroids + itraconazole

- Retrospective study

139 patients

- Average F/U 31.4 months
- Strategy:
  - Endoscopic surgery
  - Itraconazole orally, continuous
  - Topical steroids
  - Short courses of low-dose systemic steroids
- Outcome: recurrence of disease in 50% BUT the need for surgery was 21%)

Rains BM. Am J Rhinol. 2003 17(1):1-8.

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Chronic invasive fungal sinusitis

Chronic Invasive Fungal Sinusitis

- Poorly described entity
- Indolent course with soft-tissue invasion.
- Classified into two histological entities

Chronic invasive

- Invasion of vessels
- Immunocompromised and diabetics
- Caused mainly by Aspergillus fumigatus

Chronic granulomatous invasive

- Immune competent individuals
- Non-caseating granulomatous inflammation, no vessel invasion
- Reported mainly in Sudan, India and Pakistan
- Caused by Aspergillus flavus and dematiaceous fungi

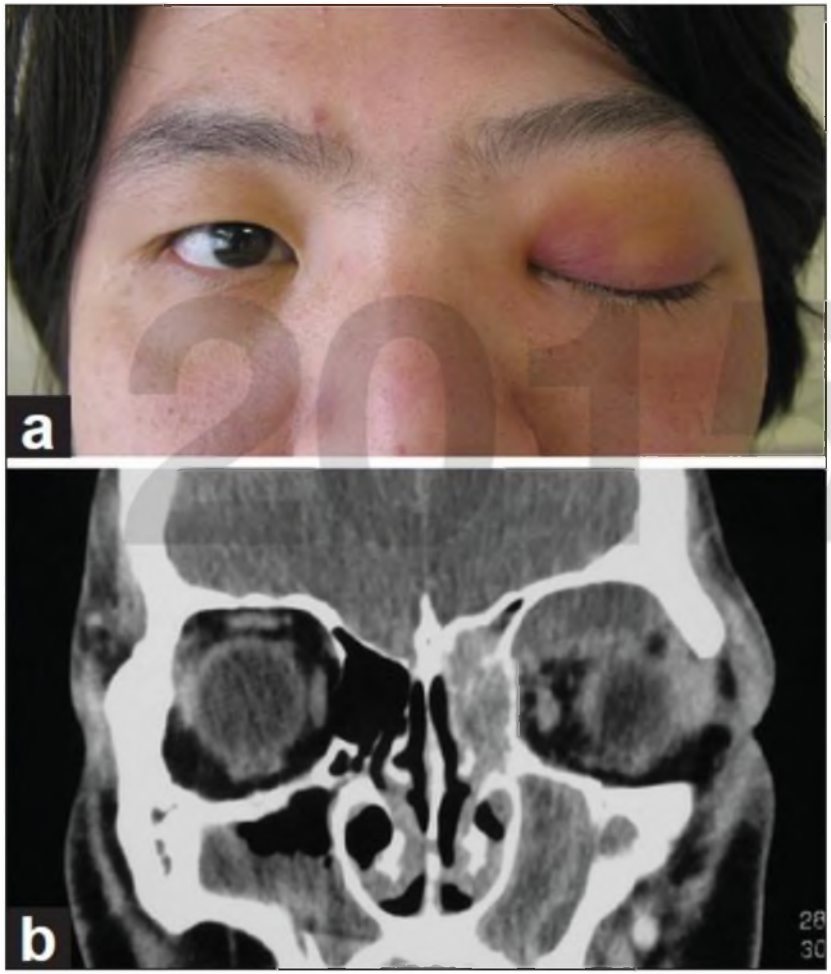
DeShazo. Arch Otolaryngo Head Nech Surg 1997; 123:1181)

Are granulomatous & chronic invasive separate entities? De Shazo *et al.*, 1997

	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	A. flavus	A. fumigatus

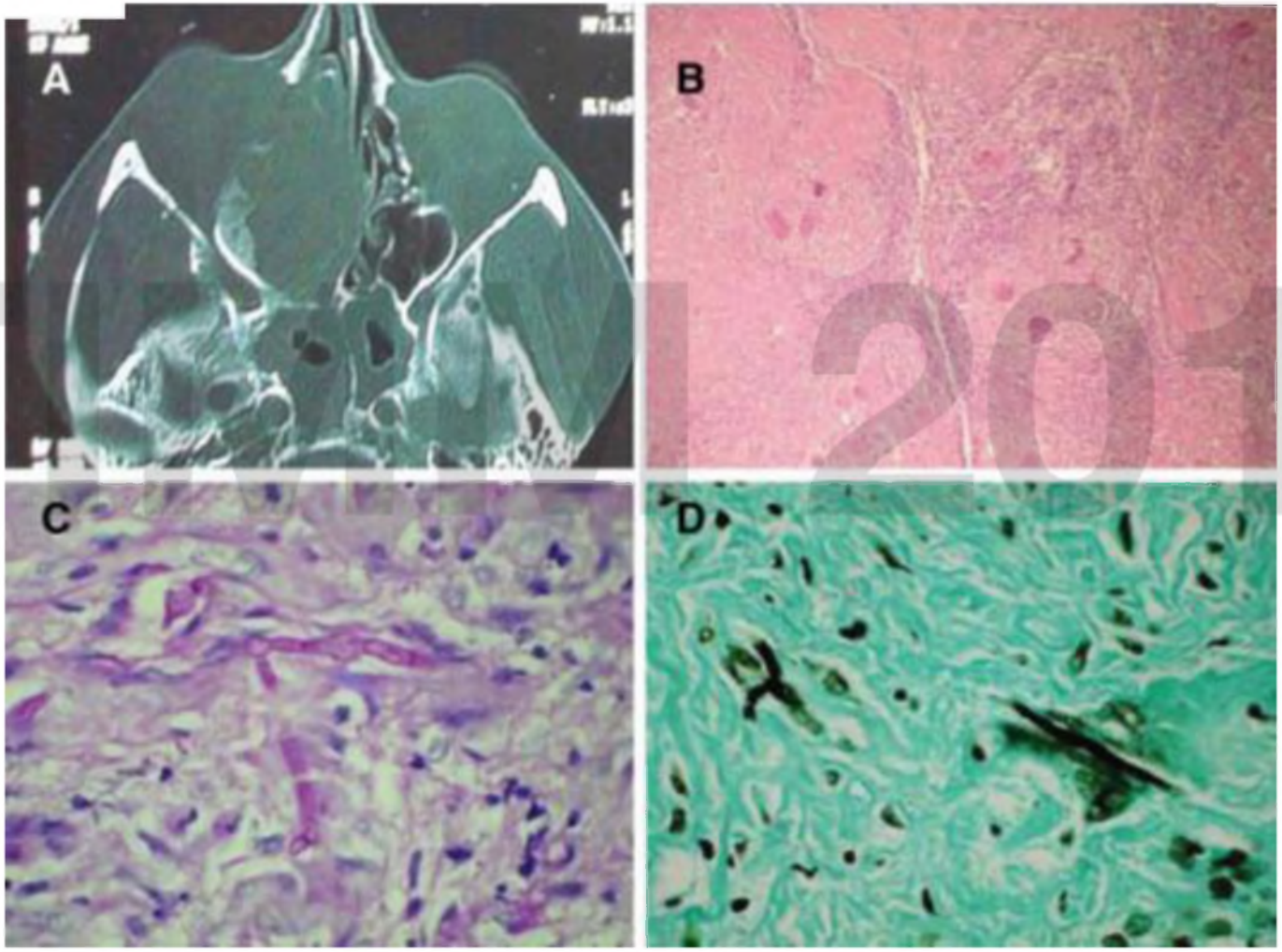
Orbital apex syndrome

Left orbital cellulitis with redness and proptosis. (b) CT scan of the same patient demonstrating opacification of left paranasal sinuses and left subperiosteal orbital abcesses of the orbital roof



- **sudden or subacute loss of vision, ophthalmoplegia**

Chronic granulomatous fungal rhinosinusitis



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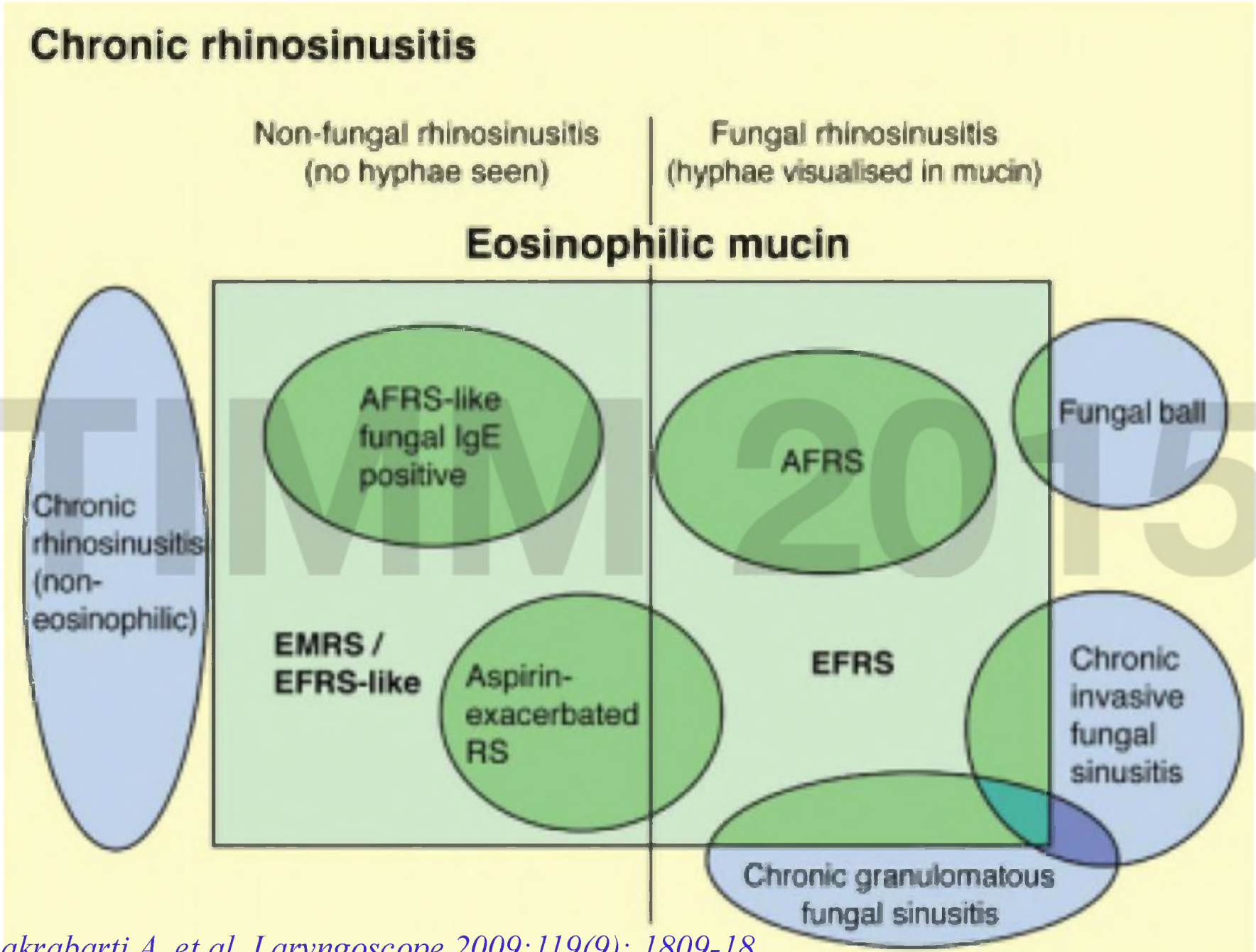
Studies still needed!!!!

- 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?

AFRS - More questions than answers

- Correct definition of AFRS
- What about EFRS, EMRS?
- Does AFRS type lead to invasive type?
- Is fungi a bystander in whole process?
- Whether these types are a spectrum of single disease?
- What about the process sino-bronchial allergic mycosis syndrome?



Chakrabarti A, et al. Laryngoscope 2009;119(9): 1809-18

Conclusions

- Fungal sinusitis is a relatively common problem
- However, confusion persists
- Understanding the nature of the disease determine the approach to therapy
- Surgery is the mainstay treatment for fungal sinusitis
- Allergic fungal sinusitis could mean a life-long relationship with the patient?
- Antifungal therapy is an absolute indication in chronic invasive fungal sinusitis and a relative indication in allergic fungal sinusitis

FSN
Fungal Sinusitis Network

ISHAM
INTERNATIONAL SOCIETY OF HUMAN AND ANIMAL MYCOLOGY

- Controversies surrounding categorization of fungal sinusitis
- 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