

# Parliamo di Malattie Granulomatose di Interesse Infettivologico

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Genoa, Italy

10 <sup>11ª edizione</sup>  
HOT TOPICS  
in infectious diseases

Genova | 22 giugno 2022

Centro Congressi Castello Simon Boccanegra  
Ospedale Policlinico San Martino

## PROGRAMMA

09:50-10:00 Apertura lavori  
M. Bassetti (Genova)

### I Sessione

Moderatori: A. Ballestrero (Genova) - G. Icardi (Genova)

10:00-10:40 COVID-19: sono già due anni. Come si cura oggi in ospedale?  
C. Dentone (Genova) | Discussant: L. Ball (Genova)

10:40-11:20 COVID-19: come si cura oggi a casa?  
A. Vena (Genova) | Discussant: S. Artioli (Spezia)

11:20-12:00 Vaccini e COVID: Chi, come, quando e perchè?  
G. Rasi (Roma) | Discussant: F. Ansaldi (Genova)

12:00-12:40 Nuovi antibiotici per la cura dei batteri MDR  
M. Bassetti (Genova) | Discussant: F. Portunato (Genova)

12:40-13:20 Nuovi metodi e nuove tecniche di diagnosi rapida  
a disposizione del clinico  
D. R. Giacobbe (Genova) | Discussant: A. Marchese (Genova)

13:20-14:20 Lunch

### II Sessione

Moderatori: E. Angelucci (Genova), D. Ferone (Genova)

14:20-15:00 Come migliorare l'approccio alla terapia di S.aureus  
M. Mikulska (Genova) | Discussant: A. Orsi (Genova)

15:00-15:40 HIV update 2022: quali nuove sfide ci attendono per vincere la  
guerra? Presente e futuro delle strategie di trattamento  
A. Di Biagio (Genova) | Discussant: G. Cenderello (Sanremo)

15:40-16:20 Il sepsis team modello Sant'Orsola  
P.L. Viale (Bologna) | Discussant: E. Arboscello (Genova)

16:20-17:00 Parliamo di malattia granulomatose di interesse infettivologico  
A. De Maria (Genova) | Discussant: R. De Palma (Genova)

17:00-17:40 Infezioni da Gram-positivi difficili: opzioni diverse per diversi settings  
F. G. De Rosa (Torino) | Discussant: G. Carrega (Savona)

17:40-17:50 Chiusura dei lavori  
M. Bassetti (Genova)

Segreteria organizzativa

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Presidente del Congresso

Professor Matteo Bassetti  
Clinica di Malattie Infettive  
Ospedale Policlinico San Martino  
Genova



# Granuloma

- localized inflammatory reaction or a hypersensitive response to a persistent foreign entity leading to
  - an organized collection of epithelioid histiocytes -a key feature of granulomas.
- This histological appearance ranges from small clusters of histiocytes, as seen in Crohn's disease, to huge well-circumscribed whorls of cells commonly appreciated in Sarcoidosis



# Granuloma composition, Necrosis

- Granulomas can have either necrotizing or nonnecrotizing features.
  - Necrotizing = infectious
  - Non-necrotizing = maybe autoimmune
- Granuloma composition can be highly variable
- Even within a single individual, infection can result in granulomas with distinct histologic features that each progress independently over time.



# Granuloma: cells and organs

- **Different cell types** constitute a granuloma (monocytes, fibroblasts, CD4+ CD8+ T cells)
- **Different tissues** are interested by different types of granuloma and with different etiologies (Lung, Intestine, Kidneys, etc)
- Granulomas need to be considered in **4 dimensions** as dynamic and different structures in : space (3D) and time.
- Infectious Granulomas Paradigm: Lung, MTB



# Infectious Granulomas

## Most commonly involved organs and pathogens

- Lung
  - Intestine
  - Skin
  - LN
- Bacterial
    - **MTB**, Bartonella (CSD, Bacillary Angiomatosis), **Yersinia**, Lymphogranuloma venereum, Syphilis, Salmonella typhi
  - Fungal
    - Histoplasmosis, Cryptococcosis, Coccidioidomycosis, Aspergillus
  - Parasites
    - Schistosomiasis, Anisakis, Leishmania



# Infectious Granulomas

## Most commonly involved organs and pathogens

- Lung

- Mycobacterial
  - MTB, NTM
- Fungi
  - Histoplasma, Cryptococcus, Coccidioides, Blastomyces, Pneumocystis, Aspergillus
- Parasites
  - Dirofilaria

- Intestine

- Bacterial
  - MTB, Bartonella (CSD, Bacillary Angiomatosis), Yersinia, Lymphogranuloma venereum, Syphilis, Salmonella typhi
- Fungal
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- Parasites
  - Schistosomiasis, Anisakis, Leishmania



# Infectious Granulomas

## Intestinal Pathogens and localizations:

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- Bacterial:
  - Mycobacterium tuberculosis
    - Ileocecum->asc.colon ->jejunum ->appendix ->sigmoidcolon
  - Bartonella henselae
    - Cat-scratch-dis: terminal ileum-colon
    - Bacillary Angioamatosis: esophagus, stomach, duodenum, colon
  - Yersinia: Terminal ileum cecum appendix, mesenteric In
  - Lymphogranuloma venereum
    - Rectum and distal colon
  - Salmonellosis: ileum, cecum, appendix right colon

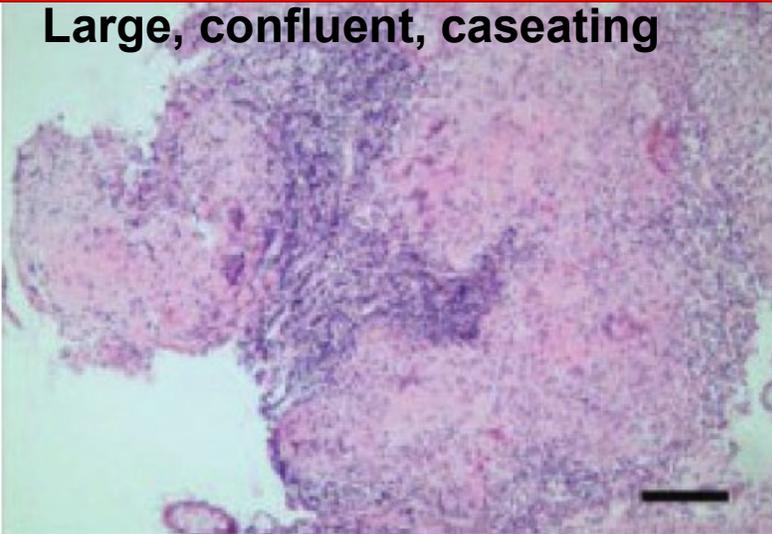
## Comparison of histological features between Mycobacterium tuberculosis, Yersinia, and Crohn's disease

Histopathological features	Tuberculosis	Yersinia spp.	Crohn's disease
Number of granulomas	Numerous	Numerous	Few
Size of granulomas	Large (>200 $\mu\text{m}$ )	Large	Small (<200 $\mu\text{m}$ )
Other granuloma features:			
(i) Caseating	Common	Few	Absent
(ii) Confluence	Common	Common	Absent
(iii) Prominent lymphoid cuff	Common	Common	Uncommon
(iv) Lymphoid hyperplasia	Common	Very common	Uncommon
(v) Architectural distortion	Common	Common	Common
(vi) Ulcers (deep and aphthous)	Common	Common	Common
(vii) Changes of chronicity unassociated with sites of granulomatous inflammation	Absent	Absent	Common
Multiple sites of involvement	Common	Rare	Common
Cobble-stoning of mucosa	Uncommon	Uncommon	Common
Fistulas	Uncommon	Rare	Common
Anal or perianal disease	Rare	Absent	Common

# Granulomas

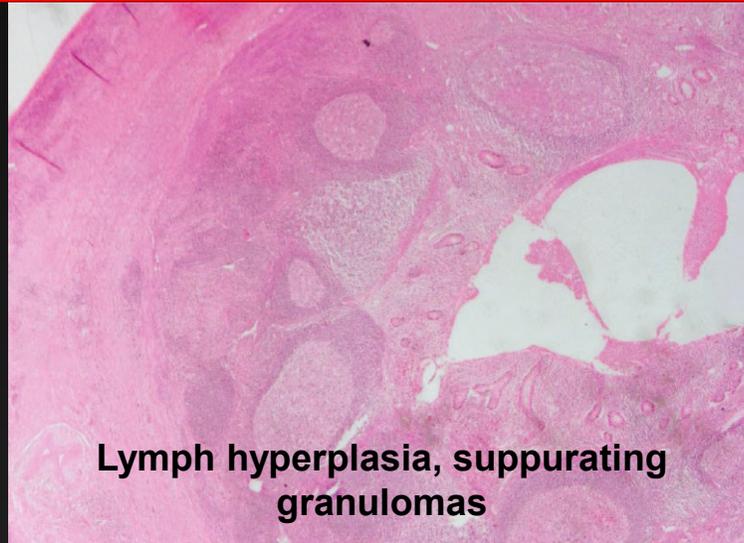
## TB

Large, confluent, caseating



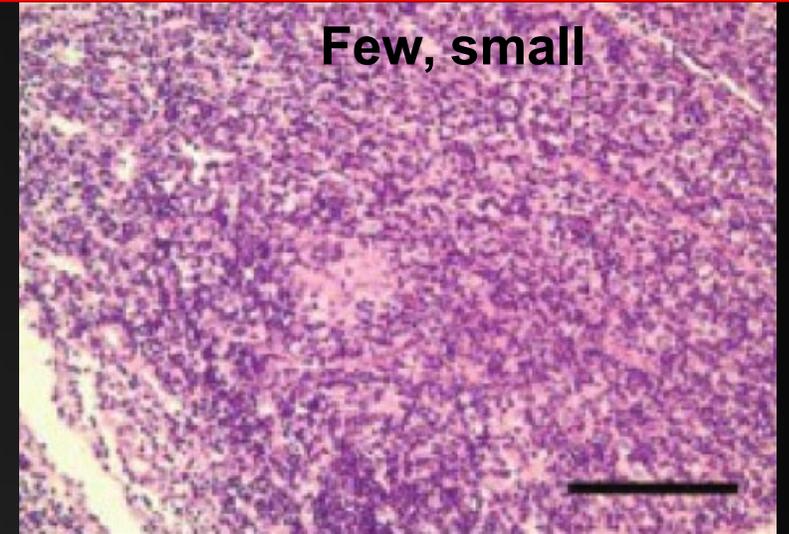
## Yersinia

Lymph hyperplasia, suppurating granulomas

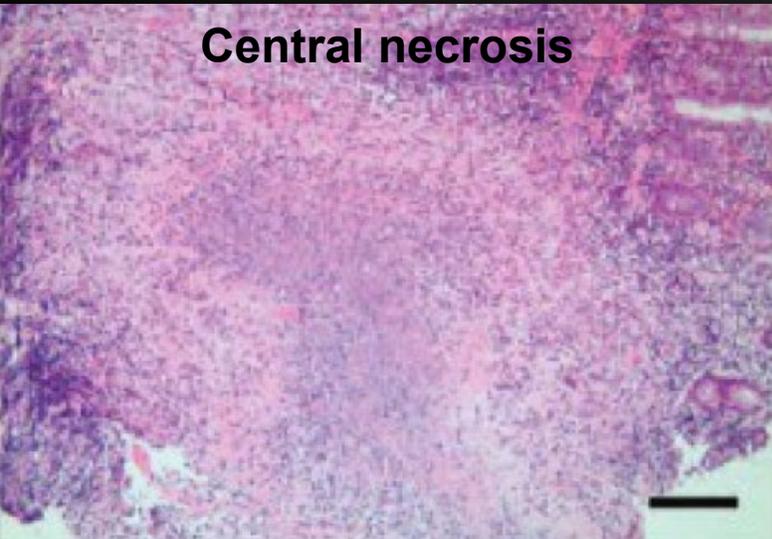


## Crohn

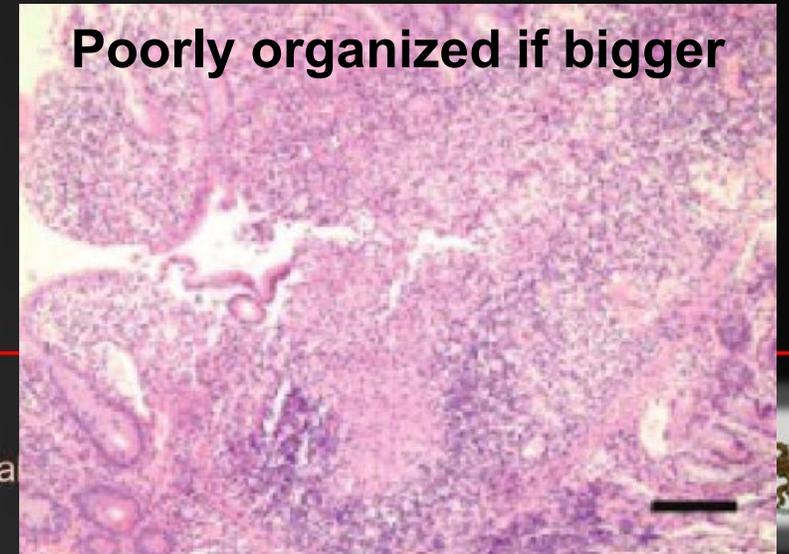
Few, small



Central necrosis



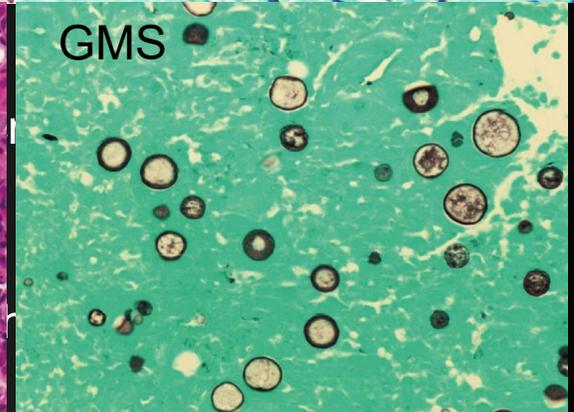
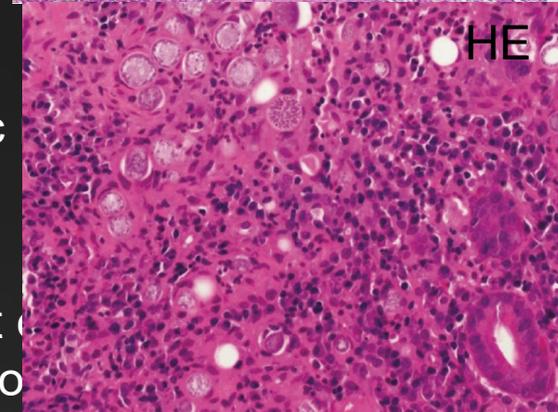
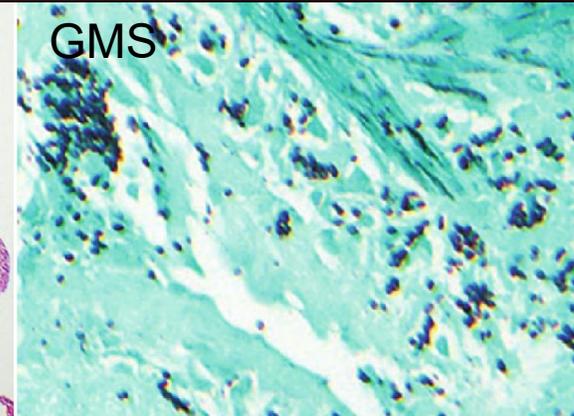
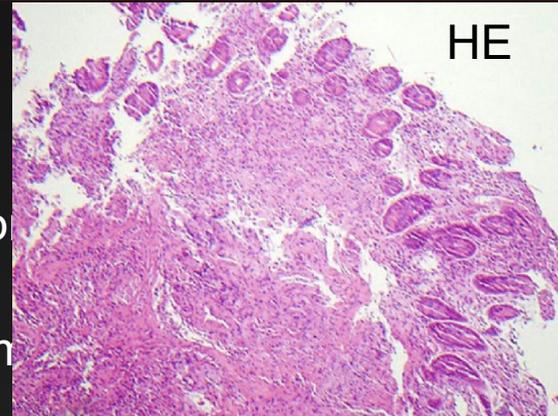
Poorly organized if bigger



# Infectious Granulomas

## Intestinal Pathogens and localizations:

- **Fungal** CT: (polypoid, omental thickening Cd)
  - Histoplasmosis,
    - Clusters of macrophages localized in the lamina propria lesions
    - noncaseating granulomas but appear fewer in number with ragged borders.
  - Cryptococcosis
    - Caseating granulomas with a moderate histiocytic lymphocytic and neutrophilic components
  - Coccidioidomycosis
    - Caseating suppurative granulomas with giant cells and spherules containing endospores and stain poorly



# Infectious Granulomas

## Most commonly involved organs and pathogens

- Lung
  - Mycobacterial
    - MTB, NTM
  - Fungi
    - Histoplasma, Cryptococcus, Coccidioides, Blastomyces, Pneumocystis, Aspergillus
  - Parasites
    - Dirofilaria



# Clinical Presentation of Granulomatous Diseases:

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## Differential Diagnosis

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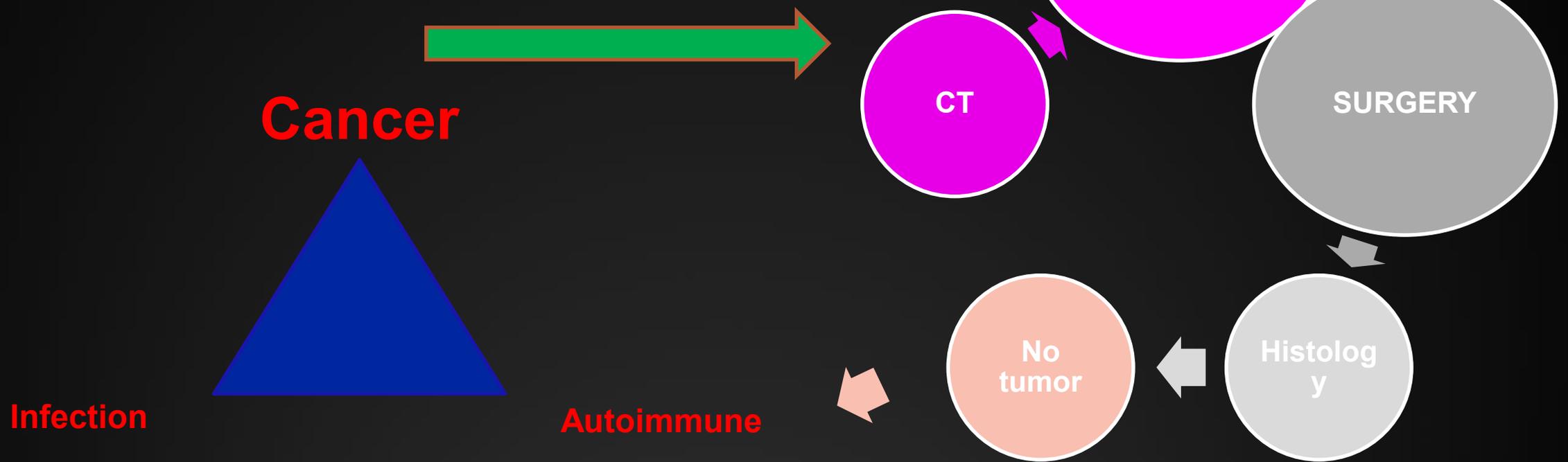
- Fever, chronic
- Systemic inflammation
  - >CRP
- Organ involvement
- Weight loss

- Cancer
- Immune-mediated disease
- Infection



# Real Life Implications in Lung Granulomatous Diseases

**Isolated Nodule or Nodule+ Infiltrate**  
Few systemic symptoms  
No culture  
No autoimmune tests or history

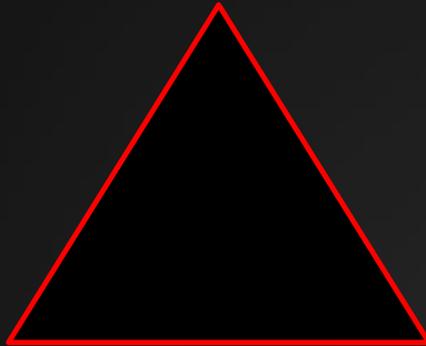


# Real Life Implications in Lung Granulomatous Diseases

**Multiple Nodules + Infiltrate**  
Some systemic symptoms  
No isolates  
No autoimmune tests or history

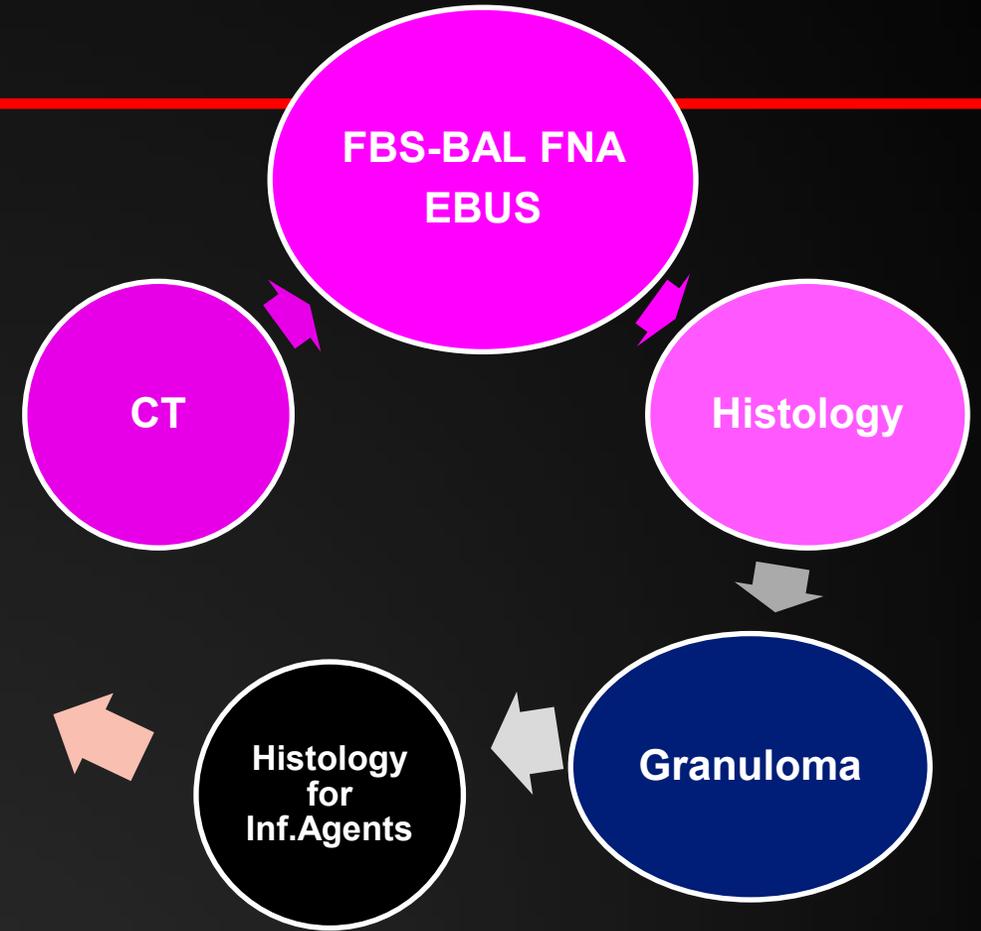


Cancer



Infection

Autoimmune



# Granulomatous lung disease

- **infectious**

- **mycobacterial**

- pulmonary tuberculosis
- pulmonary non-tuberculous mycobacterial infection

- **fungal**

- pulmonary coccidioidomycosis
- pulmonary cryptococcosis
- pulmonary histoplasmosis
- pulmonary blastomycosis
- pulmonary aspergillus infection

- **parasitic**

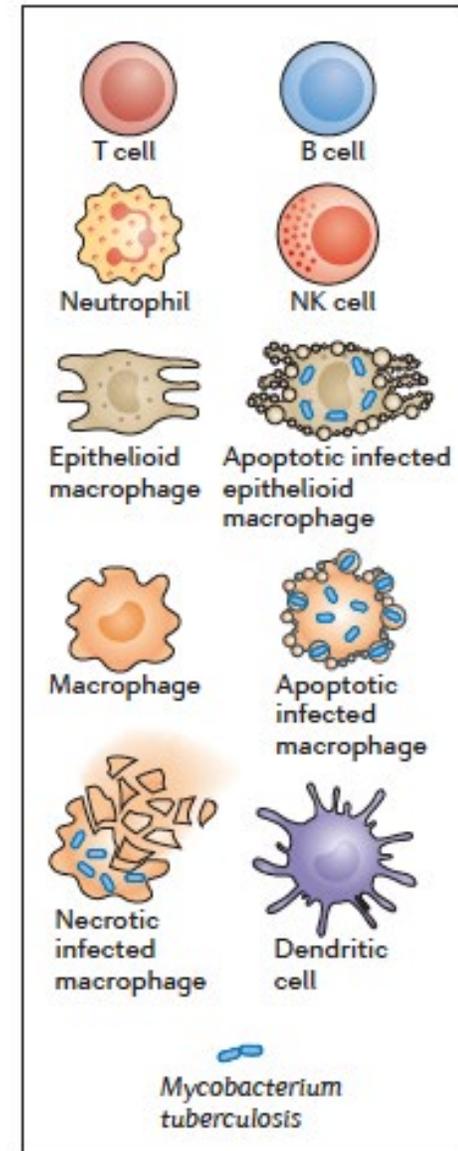
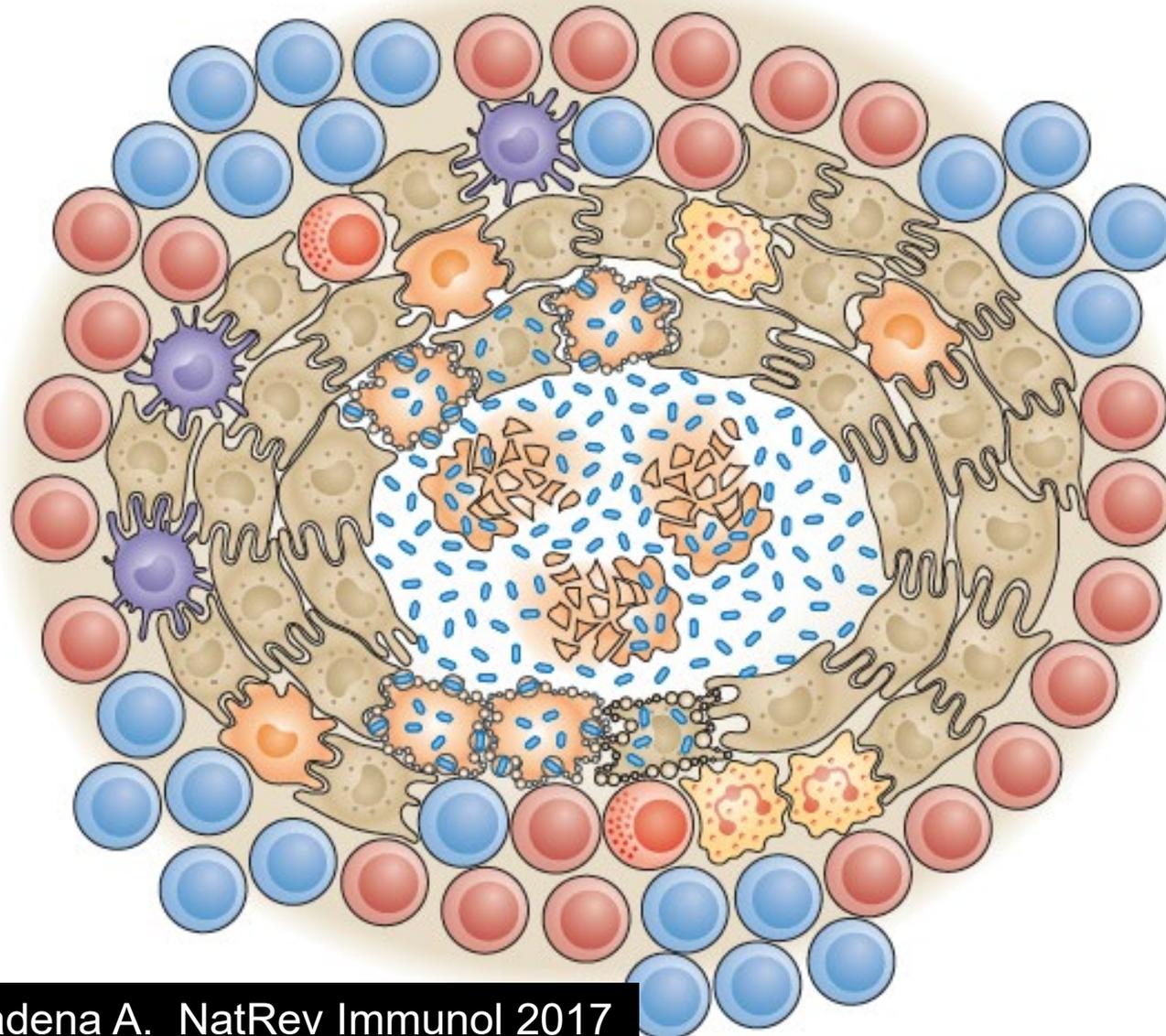
- pulmonary dirofilaria infection

- **non-infectious**

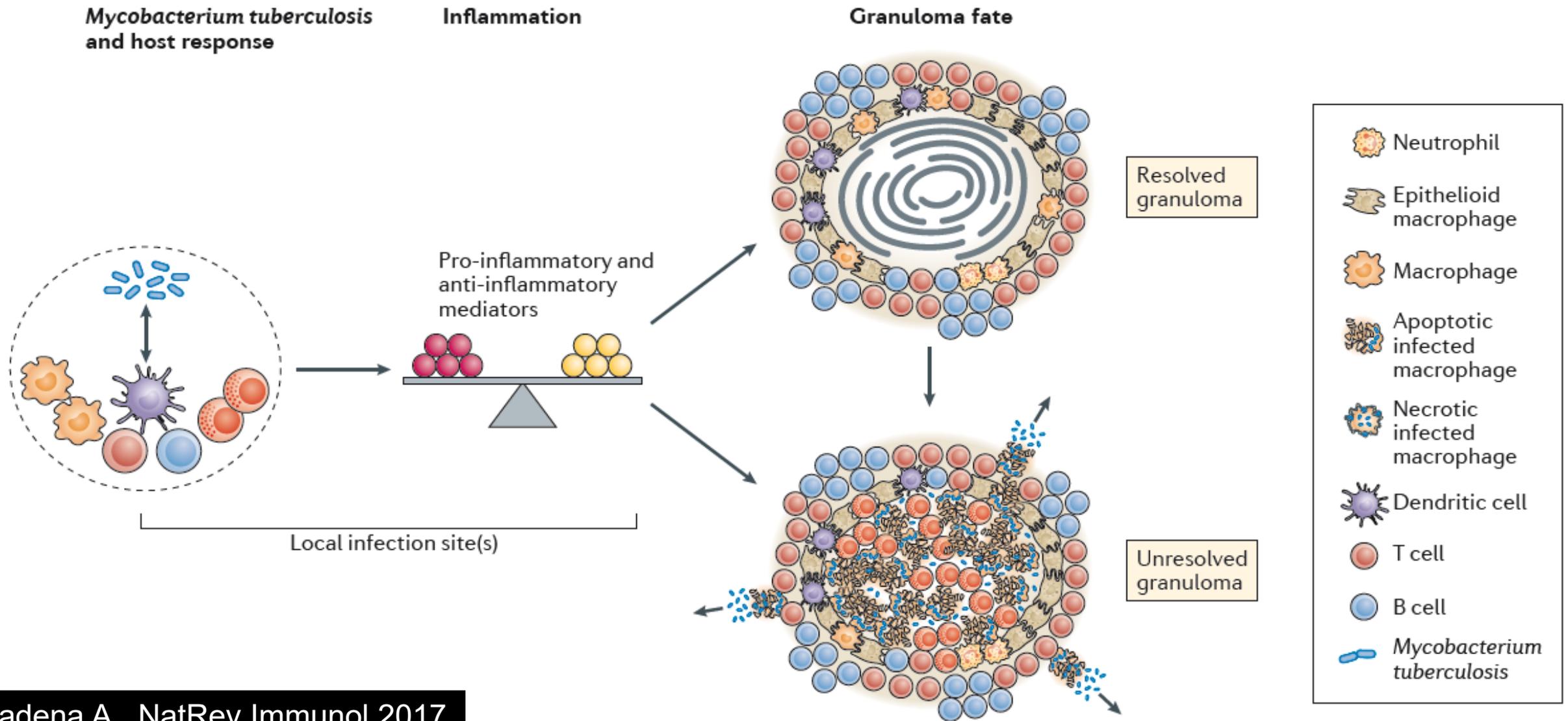
- pulmonary sarcoidosis
  - necrotizing sarcoid granulomatosis
- ANCA-associated
  - granulomatosis with polyangiitis
  - Churg-Strauss syndrome
- chronic granulomatous disease <sup>2</sup>
- hypersensitivity pneumonitis
- bronchocentric granulomatosis
- pulmonary manifestations of rheumatoid arthritis
  - rheumatoid lung nodules
- granulomatosis secondary to substances
  - pulmonary talc granulomatosis
  - berylliosis
  - granulomatous pneumonitis associated with BCG vaccination
- changes secondary to chronic aspiration pneumonitis
- lymphoproliferative
  - lymphocytic interstitial pneumonitis
  - lymphomatoid granulomatosis
- pulmonary Langerhans cell histiocytosis
- Erdheim-Chester disease
- granulomatous lung disease associated with common variable immunodeficiency



# Composition of a paradigm granuloma: MTB in the Lungs



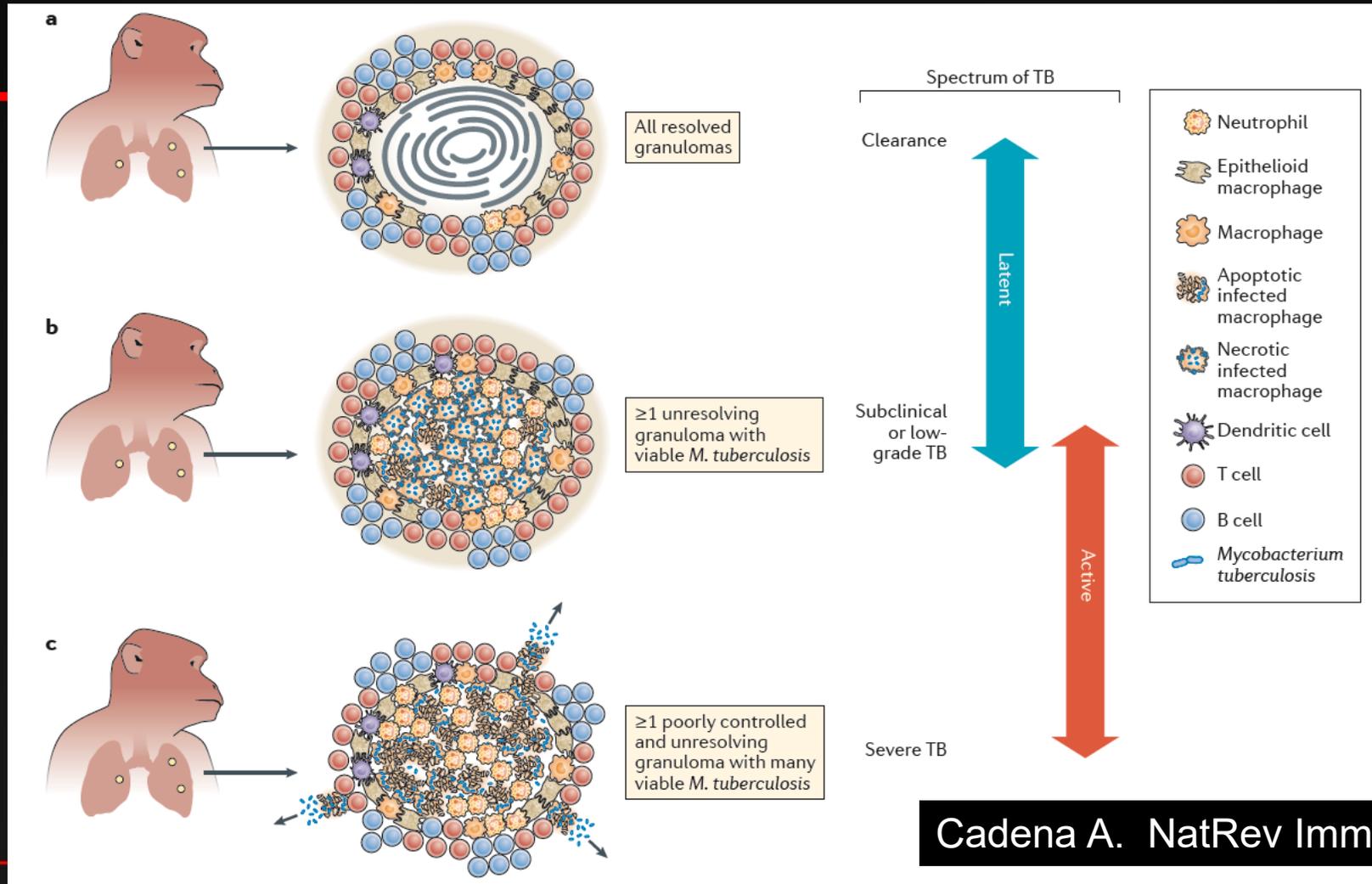
# In the lungs, a crucial interplay between the bacteria and host immune cells influences inflammatory programmes that contribute to granuloma outcome



Cadena A. NatRev Immunol 2017

This process is highly dynamic and iterative, with multiple components having pleiotropic, knock-on and feedback effects on inflammation and the host-pathogen interaction

# Individual granulomas establish variable host outcomes and contribute to the overall spectrum of tuberculosis



Cadena A. NatRev Immunol 2017



- efforts to develop new host-directed therapies to treat TB disease have been **hindered by an incomplete understanding of how the human immune system responds to *Mtb***
- Engulfment of MTB in phagocytes triggers an immune response that converges on formation of a granuloma, a **dynamic and spatially organized** tissue structure composed of macrophages, granulocytes, lymphocytes and fibroblasts.



- From the perspective of facilitating an effective host response, **granulomas play contradictory roles**.
- On one hand, consolidation of infected cells within the myeloid core limits dissemination by **partitioning them away** from uninvolved lung parenchyma.
- On the other, tolerogenic pathways upregulated within this region may **limit bacterial clearance**



**OPEN**  
**The immunoregulatory landscape of human tuberculosis granulomas**

Erin F. McCaffrey<sup>1</sup>, Michele Donato<sup>2,3</sup>, Leeat Keren<sup>4</sup>, Zhenghao Chen<sup>5</sup>, Alea Delmastro<sup>1</sup>, Megan B. Fitzpatrick<sup>6</sup>, Sanjana Gupta<sup>2,3</sup>, Noah F. Greenwald<sup>1</sup>, Alex Baranski<sup>1</sup>, William Graf<sup>7</sup>, Rashmi Kumar<sup>1</sup>, Marc Bosse<sup>1</sup>, Christine Camacho Fullaway<sup>1</sup>, Pratista K. Ramdial<sup>8</sup>, Erna Forgó<sup>1</sup>, Vladimir Jojic<sup>5</sup>, David Van Valen<sup>7</sup>, Smriti Mehra<sup>9</sup>, Shabaana A. Khader<sup>10</sup>, Sean C. Bendall<sup>1</sup>, Matt van de Rijn<sup>1</sup>, Daniel Kalman<sup>11</sup>, Deepak Kaushal<sup>12</sup>, Robert L. Hunter<sup>13</sup>, Niaz Banaei<sup>14</sup>, Adrie J. C. Steyn<sup>8,15</sup>, Purvesh Khatri<sup>2,3</sup> and Michael Angelo<sup>1,16</sup>

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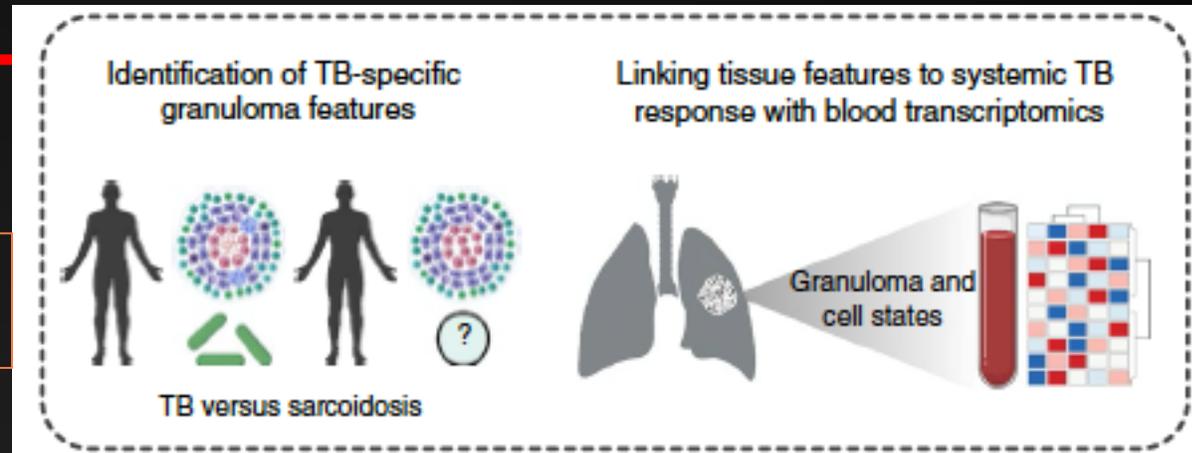
**Granuloma myeloid cells express an immunoregulatory program.**

**Granuloma lymphocytes are sparsely activated.**

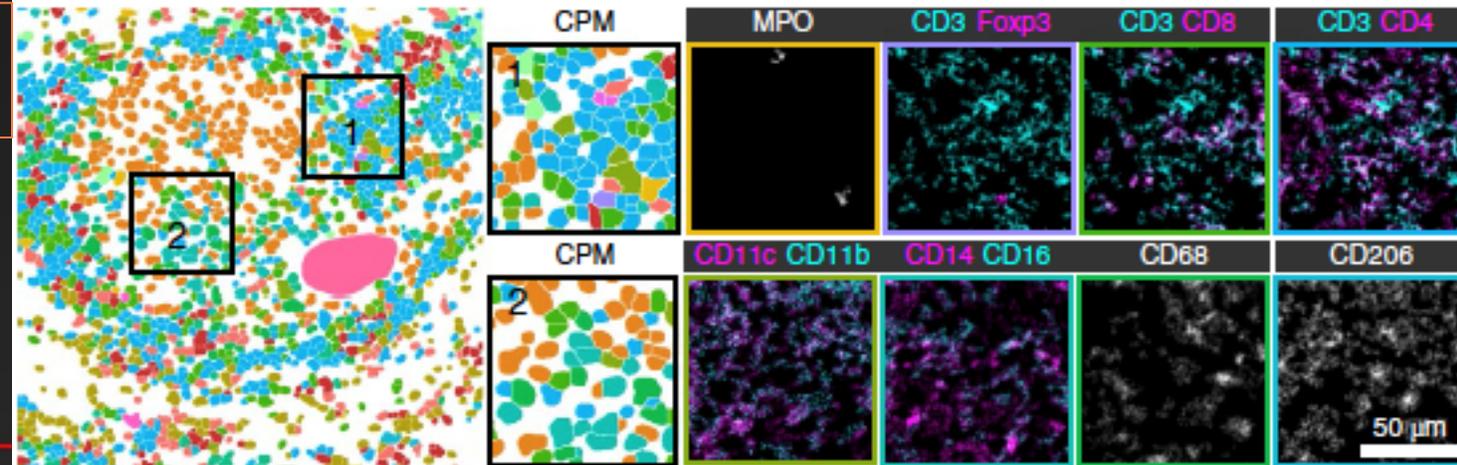
**Common and diverging immunoregulatory features in TB and sarcoidosis.**

**Immunoregulatory features are reflected across granulomas and blood.**

multiplexed ion beam imaging by time of flight (MIBI-TOF) comprehensive atlas maps 19 cell subsets across 8 spatial microenvironments



Cell phenotype map (CPM)



- CD4 T cell
- 11b/c<sup>+</sup>206<sup>+</sup> mac
- Endothelial
- Epithelial
- Mast cell
- CD8 T cell
- CD11c<sup>+</sup> DC/mono
- CD68<sup>+</sup> mac
- Neutrophil
- T<sub>reg</sub>
- CD14<sup>+</sup> mono
- CD14<sup>+</sup> CD16<sup>+</sup> mono
- CD206<sup>+</sup> mac
- CD209<sup>+</sup> DC
- γδ T cell
- B cell
- Other immune
- Fibroblast
- CD163<sup>+</sup> mac
- Giant cell



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# Granulomatous lung disease

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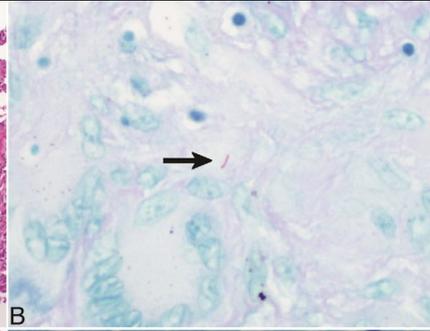
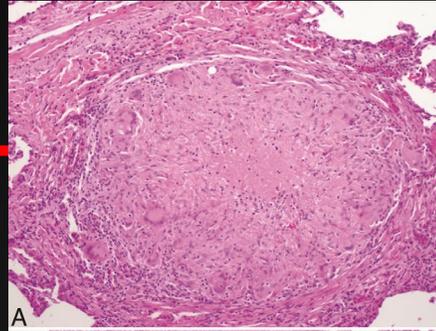
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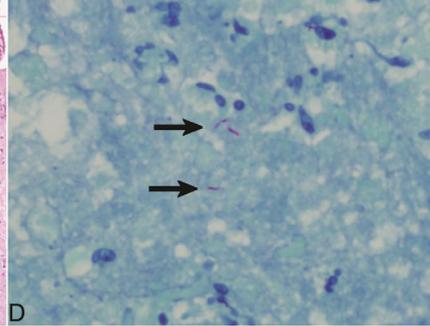
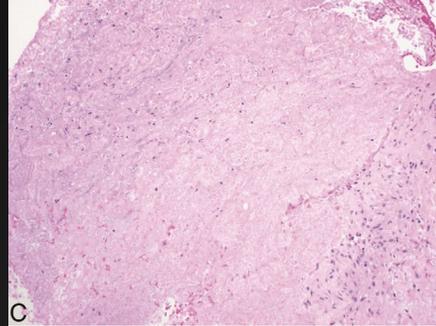


MTB



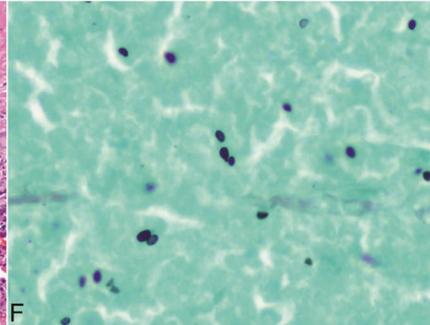
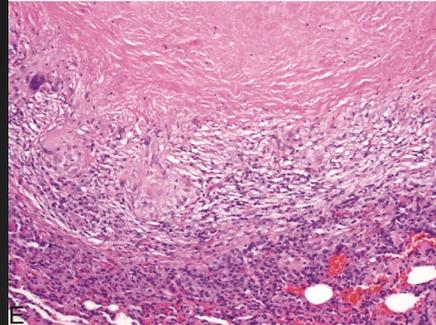
MTB

NTM (MA-I)



NTM (MA-I)

Histoplasma



Histoplasma

**Figure Legend:**

Infectious necrotizing granulomas. A, Tuberculosis. Necrotizing granuloma. B, Same case as A. Single acid-fast bacterium (arrow). C, Nontuberculous mycobacterial infection. Mycobacterium intracellulare was isolated in cultures. Necrotizing granuloma with abundant necrosis, indistinguishable from tuberculosis. Epithelioid histiocytes are at bottom right. D, Same case as C. Mycobacteria (arrows) are identical in morphology to the single organism seen in B. E, Histoplasmosis. Necrotizing granuloma larger than, but otherwise identical to, the granulomas in A and C. F, Same case as E. Histoplasma yeasts (Grocott methenamine silver, original magnification  $\times 400$  [F]).



Histoplasma

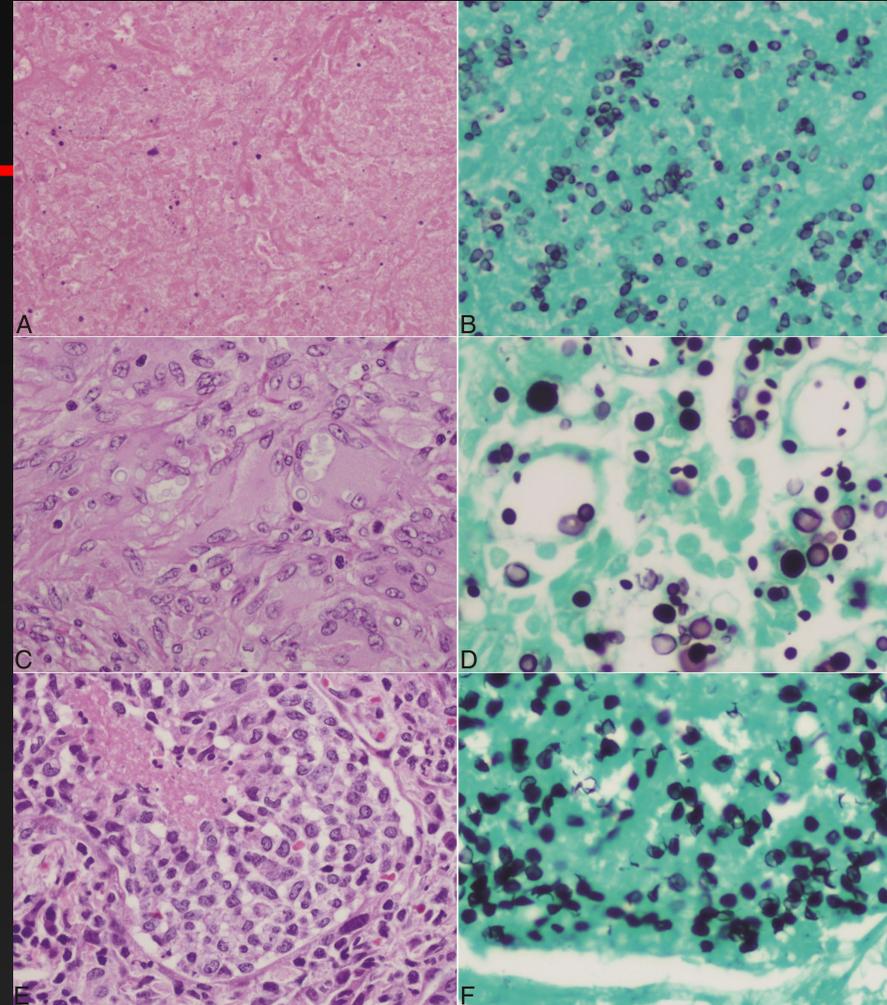
Histoplasma

Cryptococcus

Cryptococcus

PCJ

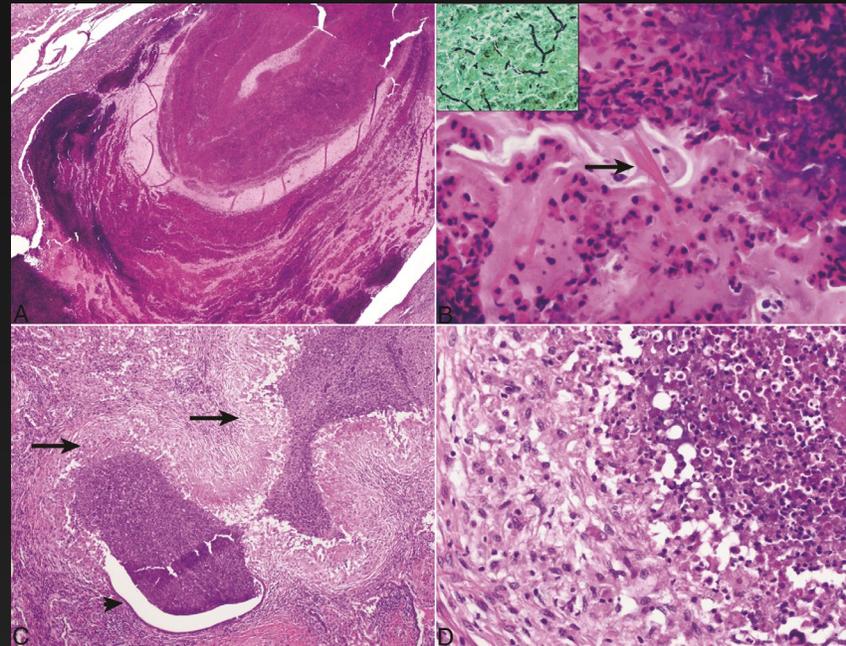
PCJ



**Figure Legend:**

Fungal granulomas. A, Necrotic center of a histoplasmosis. Organisms are not visible on a hematoxylin-eosin stain, even at high magnification. B, Same case as A. Uniform, mostly oval Histoplasma yeasts are clearly visible on a silver stain. Note that some organisms are tapered at one or both ends. C, Nonnecrotizing granulomas containing Cryptococcus. Round yeasts with blue-gray cell walls are visible within histiocytes. Note the characteristic "halo" around the organisms. D, Same case as C. Note the mostly round shape and marked variation in size. E, Granulomatous Pneumocystis pneumonia. Histiocytes palisade loosely around an intra-alveolar eosinophilic exudate. F, Same case as E. Small, round, yeastlike Pneumocystis cysts within an alveolar space. Crescentlike forms are characteristically seen (hematoxylin-eosin, original magnifications  $\times 400$  [A, C, and E]; Grocott methenamine





**Figure Legend:**

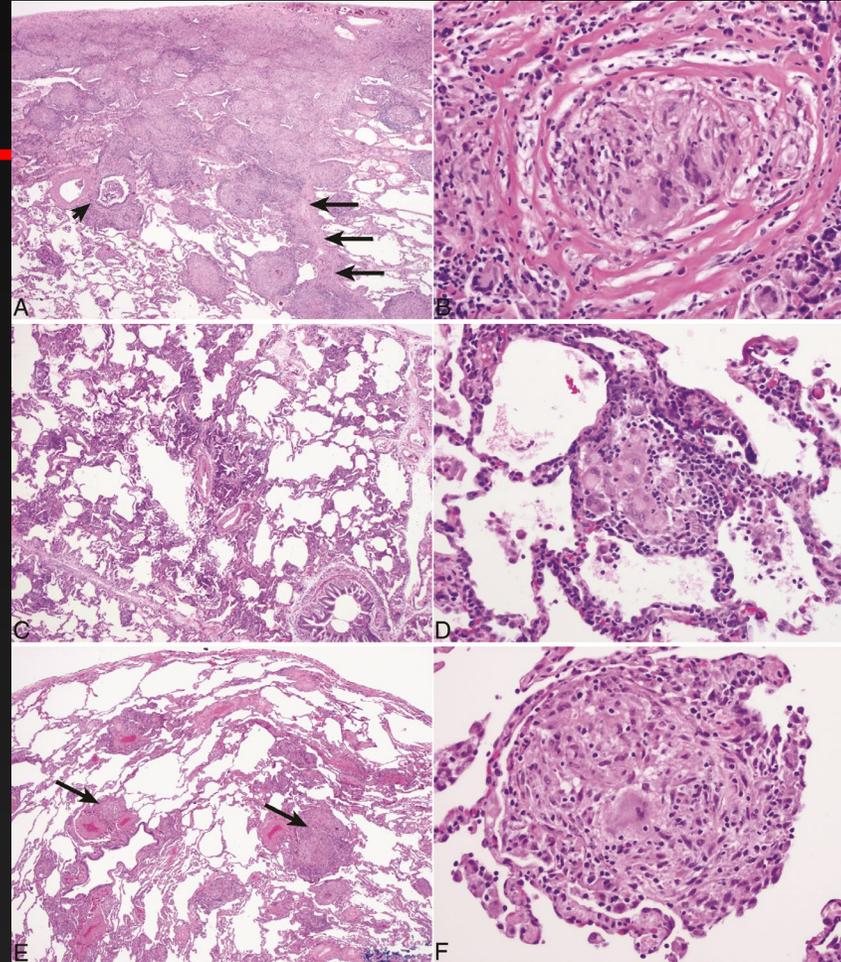
Allergic bronchopulmonary aspergillosis. A, Mucoïd impaction of bronchi. A dilated bronchus is filled with lamellated, eosinophilic debris. B, Same case as A. The intrabronchial debris is composed of necrotic eosinophils and mucus. Note characteristic Charcot-Leyden crystals (arrow). Branching hyphae are present within the debris (inset). C, Same case as A, showing bronchocentric granulomatosis. Necrotizing granulomatous inflammation (arrows) destroying a bronchiole (arrowhead). Note the necrotic debris filling the bronchiolar lumen. D, Same case as A showing a bronchocentric necrotizing granuloma at high magnification. Palisading histiocytes at bottom left, necrosis rich in eosinophils at top right (hematoxylin-eosin, original magnifications  $\times 20$  [A],  $\times 400$  [B],  $\times 40$  [C],  $\times 200$  [D]; Grocott methenamine silver, original magnification  $\times 400$  [B, inset]).



Sarcoidosis

H.Pneumonia

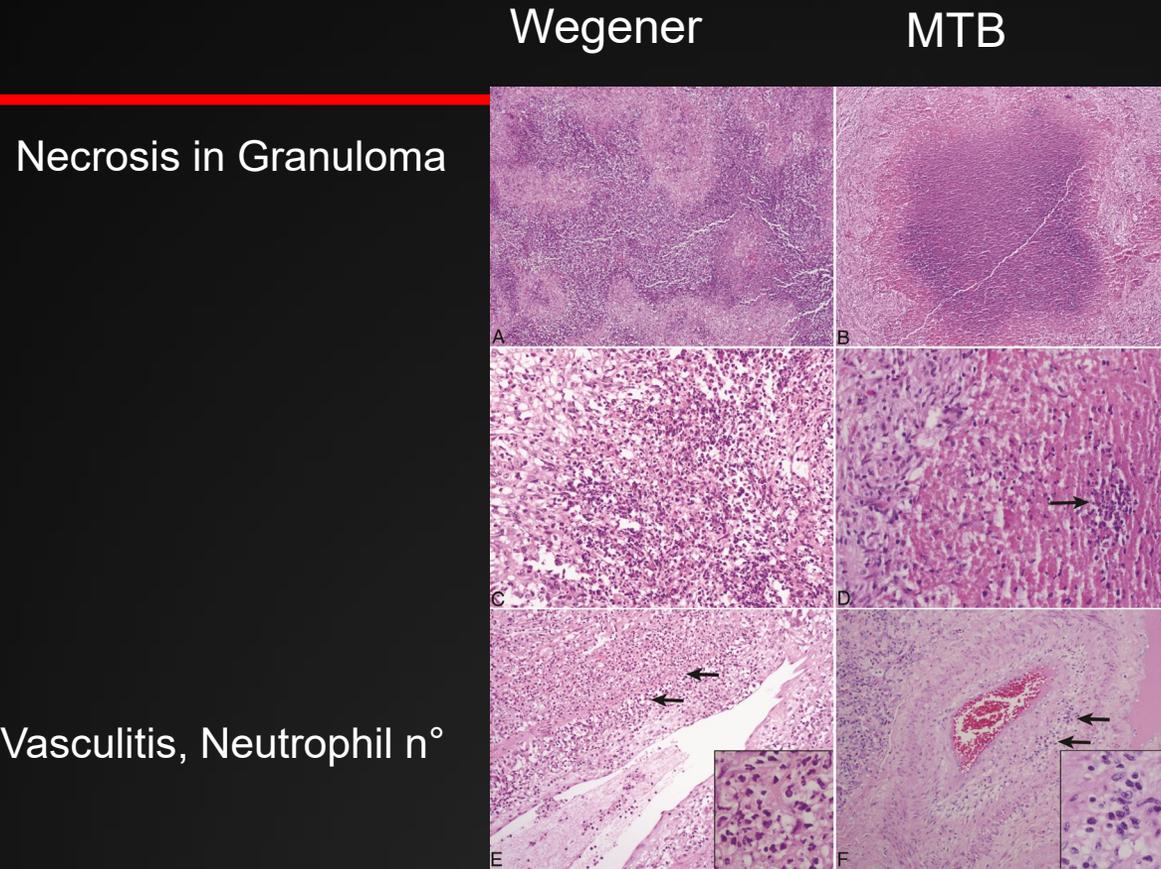
Hot tub lung



**Figure Legend:**

Noninfectious nonnecrotizing granulomas. A, Sarcoidosis. Granulomas are distributed along the pleura (top), interlobular septum (arrows) and bronchovascular bundles (arrowhead) (“lymphangitic distribution”). The inflammation is localized to the granulomas and does not extend into the adjacent lung parenchyma. B, Sarcoidosis. Well-formed, nonnecrotizing granuloma surrounded by characteristic concentric fibrosis. C, Hypersensitivity pneumonitis. The main abnormality is mild thickening of the alveolar septa (interstitium). Granulomas are not visible at this magnification. D, Hypersensitivity pneumonitis. Interstitial chronic inflammation with a loose cluster of histiocytes (poorly formed granuloma). E, Hot tub lung. The granulomas show a predilection for bronchioles (arrows). F, Hot tub lung. A well-formed, nonnecrotizing granuloma is seen within an air space (hematoxylin-eosin, original





**Figure Legend:**

Wegener granulomatosis (left) compared with an infectious granuloma (right). A, Wegener granulomatosis. Basophilic, “dirty” necrosis with irregular contours. B, Mycobacterial granuloma. Necrotizing granuloma with “dirty” necrosis but more regular contours than A. C, Same case as A. Suppurative necrosis with a rim of palisading histiocytes. D, Same case as B. Neutrophils are present within the necrotic area (arrow) but are fewer than in C. E, True vasculitis in Wegener granulomatosis, same case as A. The top portion of the vessel wall is destroyed by an inflammatory infiltrate (arrows). The infiltrating cells are predominantly neutrophils (inset). F, Same case as B. Mild nonnecrotizing vasculitis (arrows) in a case of mycobacterial infection. Vessel wall is thickened by edema and a few inflammatory cells (arrows). The inflammatory cells are predominantly lymphocytes (inset) (hematoxylin-eosin,



# Differential Diagnosis of Granulomatous Lung Disease

- Clinical presentations
  - Overt disease and extrapulmonary manifestations
  - Localized Disease
- Procedures
  - Transbronchial biopsy vs. Surgical (wedge, lobectomy)
- Immuno-chemical
  - Serology (ACE, ANCA, FR, etc.)
  - BAL immunophenotype

## Infections

### Mycobacteria

*Mycobacterium tuberculosis*

Nontuberculous mycobacteria

### Fungi

*Histoplasma*

*Cryptococcus*

*Coccidioides*

*Blastomyces*

*Pneumocystis*

*Aspergillus*

### Parasites

*Dirofilaria*

## Noninfectious diseases

Sarcoidosis

Chronic beryllium disease

Hypersensitivity pneumonitis

Hot tub lung

Lymphoid interstitial pneumonia

Wegener granulomatosis

Churg-Strauss syndrome

Aspiration pneumonia

Talc granulomatosis

Rheumatoid nodule

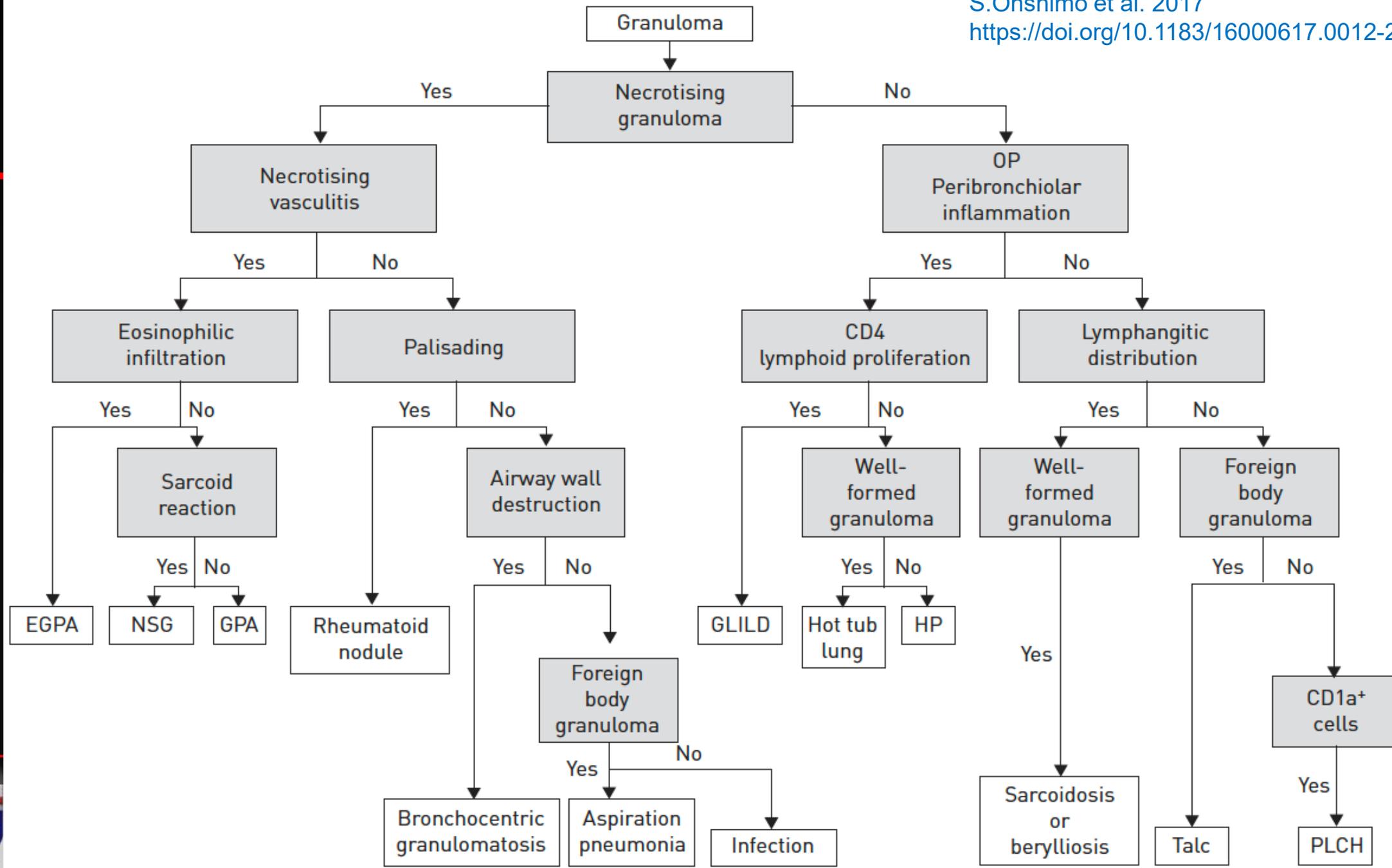
Bronchocentric granulomatosis



# Shortcomings

- PCR for Mycobacteria and fungi : not routine , not Pathology
  - Lack of integrated system striving to end diagnosis
- Clinical signs > autoimmune markers
  - Peripheral and tissue immunohistochemistry markers
- Clinical skewing based on dominant symptoms
- Time & Effort

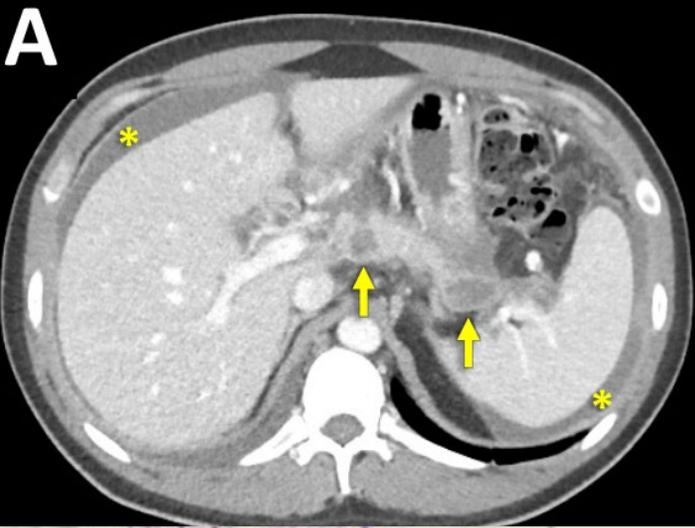




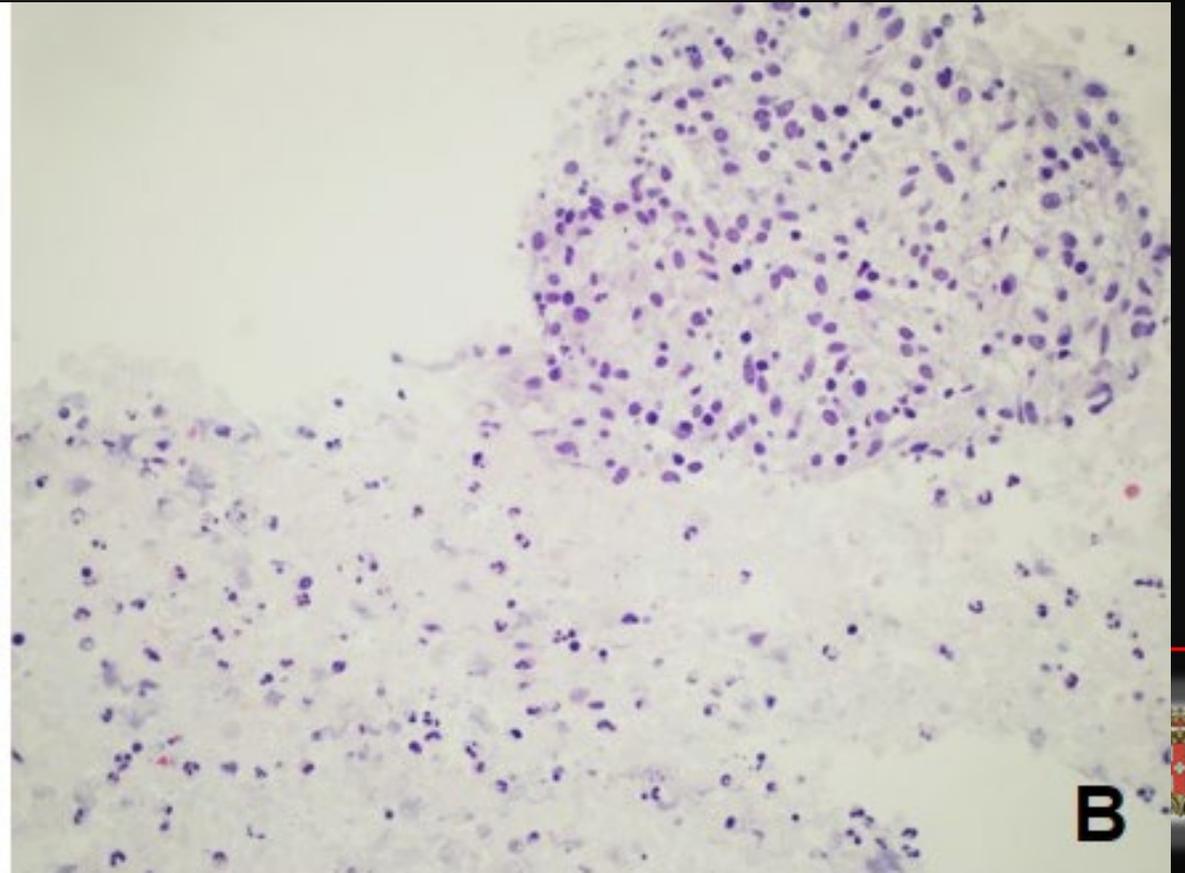
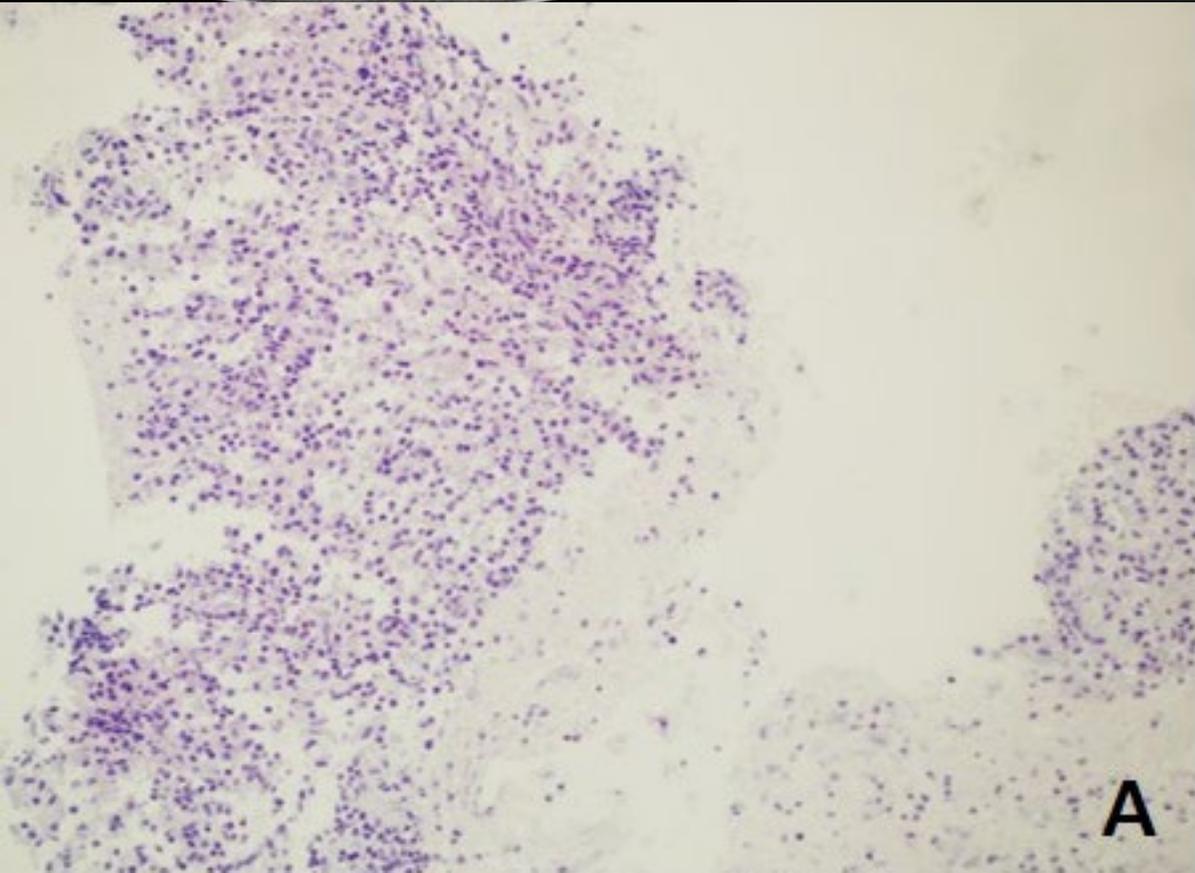
# Take home messages

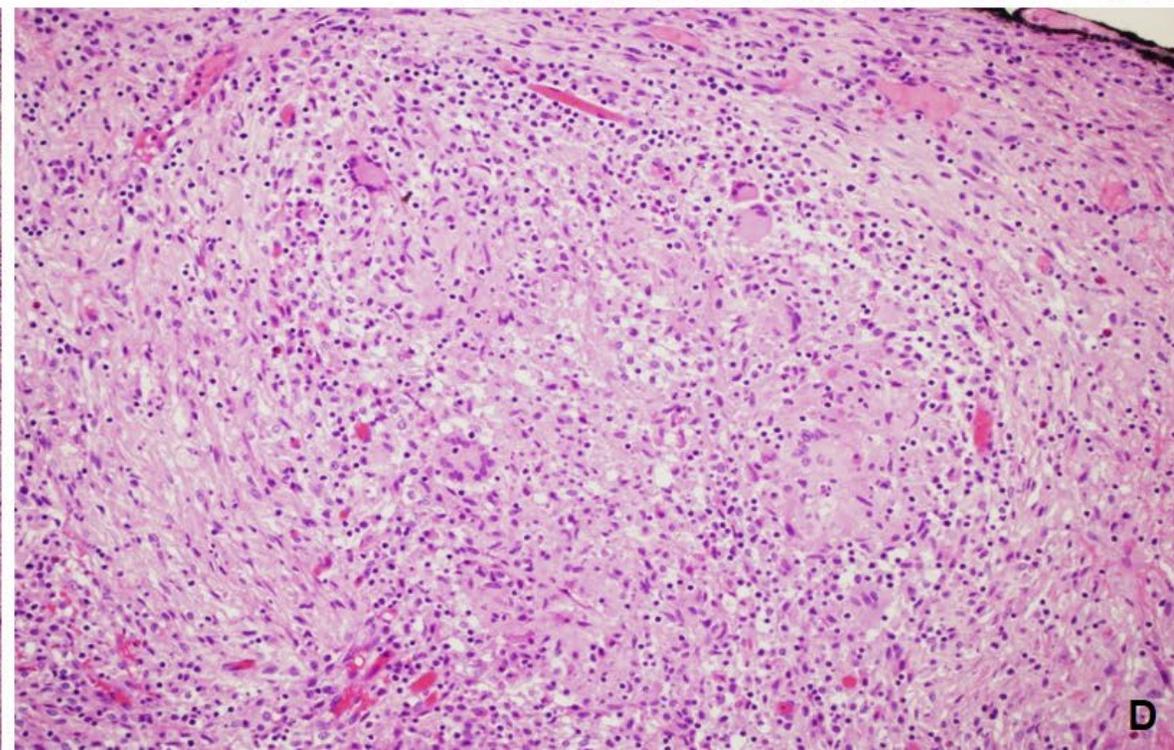
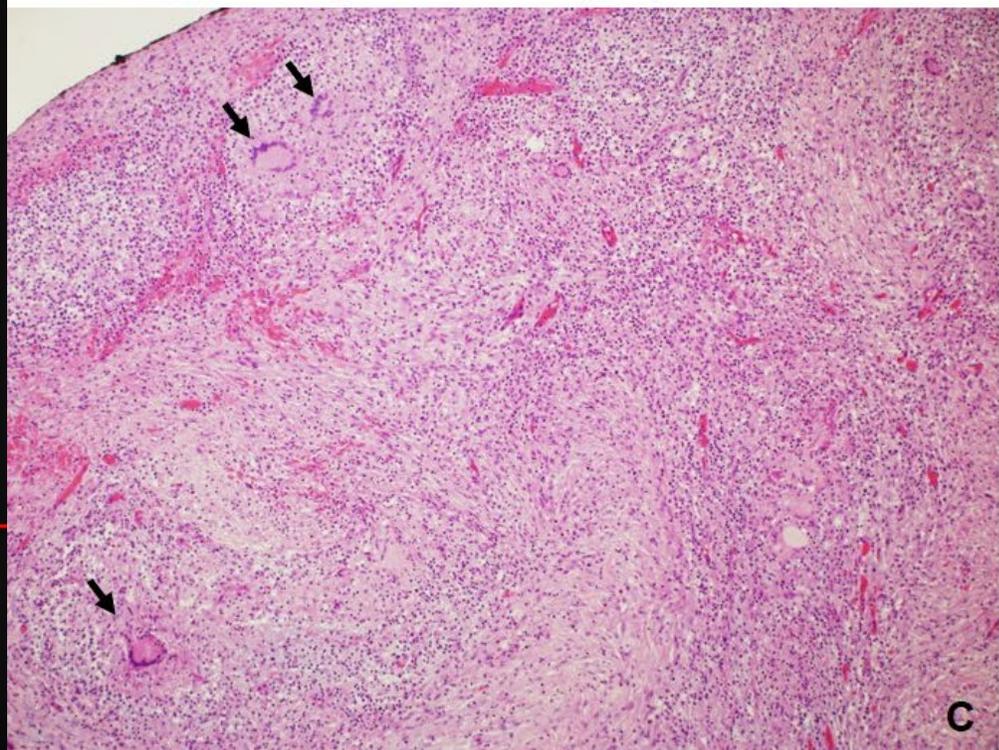
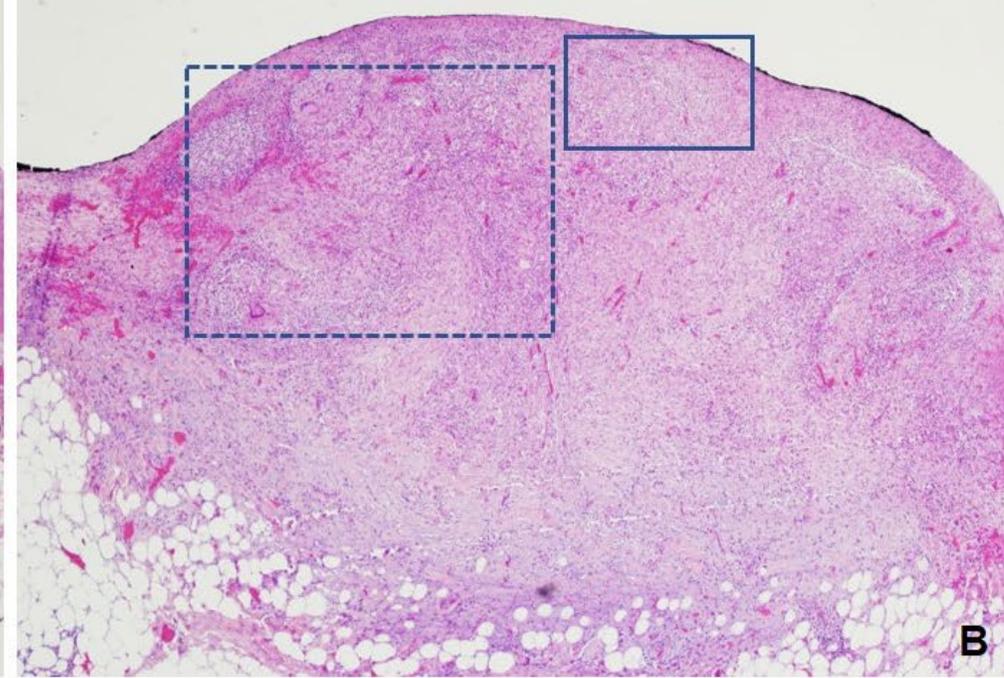
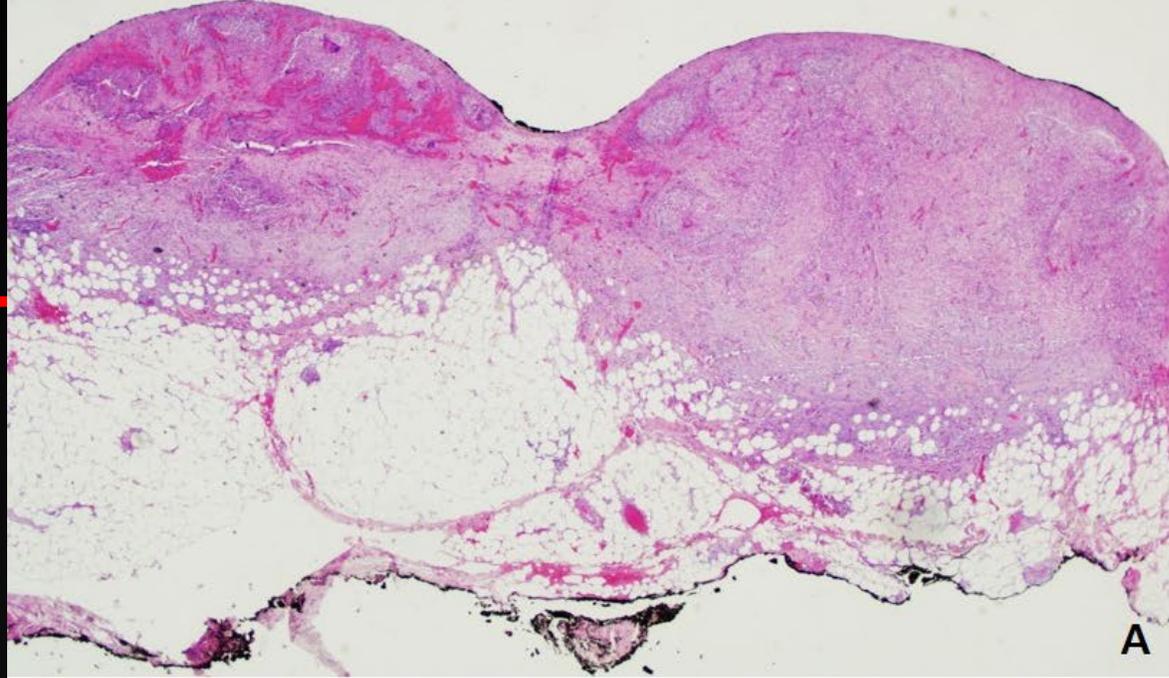
- Spesso bias iniziale
  - workup per tumore, Istologia negativa per infezione
- La biopsia è la base della diagnosi
  - La clinica e gli esami sierologici possono indirizzare, ma non dirimenti
- L'istologia indirizza il ragionamento diagnostico
  - Necrosi vs non necrosi





Fine-needle biopsy of pancreatic lesion showing a mixed inflammatory infiltrate with lymphocyte, plasma cells, histocytes, and necrotic debris (magnification 20x and 40x, panels A and B, respectively)





# Take home messages

- Necessaria sempre una diagnostica molecolare per funghi e miceti in presenza di
  - Assenza di tumore
    - Assenza di funghi o miceti in istologia
      - Overlap syndrome con reazione granulomatosa immunomediata
      - Anche senza necrosi centrale.....



# Grazie

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