TBM; Immunopathogenesis

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What kills TBM patients?

- vascular pathology & hypoxia?
- failure to control *M. tuberculosis* growth?
- 'collateral damage' to critical structures?

- what characterises effective and damaging host immune response in TBM patients?
- and what goes wrong at a cellular level?

- and how much of this is genetically determined?
  or can we use genetics to sort cause and effect and identify targets for therapy?

Patients
‘clinical phenotyping’

known / unknown immunodeficiencies or clinical immunopathology

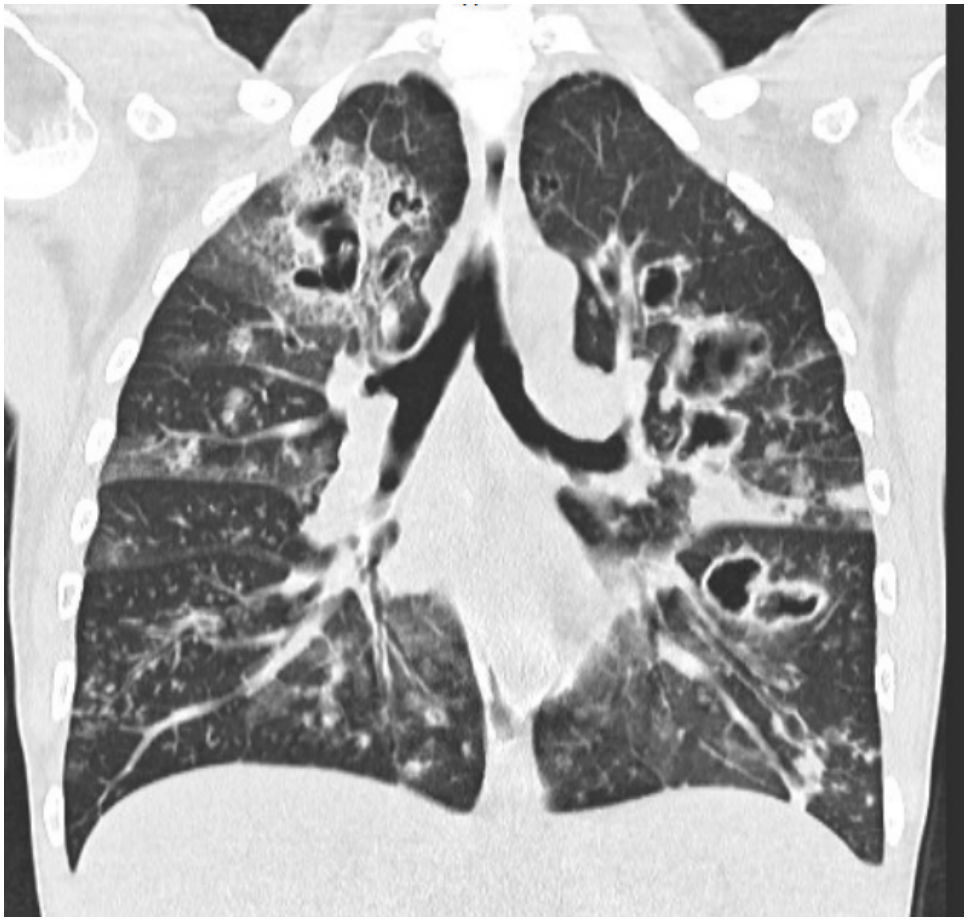
Laboratory
‘immune phenotyping’

Immunological phenotyping and/or genetics

adjuvant therapy

Immune inhibition or stimulation

excessive inflammation (38 female)



- No medical history
- Respiratory infection
- Deterioration over course of 1 month despite multiple courses of antibiotics
- Respiratory failure

- Referral:
- CRP 276. 44 leukocytes, 1% lympho's, 90% PMN
- Ferritin of 16000
- Progressive anemia and trombopenia

- Influenza and aspergillus

Macrophage activation syndrome

- Hematologists: hemophagocytic lymphohistiocytosis
- Primary (kids; mutations affecting cytotoxic T-cells/NK)
- Secondary, triggered by
  - Malignancy (lymphoma)
  - Auto-immune (juvenile RA, Still's disease, SLE ..) *termed MAS*
  - Infection (EBV, CMV, influenza…); bacterial
  - Also described in tuberculosis

- Excessive but ineffective immune activation
  - *Fever*
  - *hepatosplenomegaly*
  - *Lymphadenopathy*
  - *hemophagocytosis*

- *Cytopenia*
- *High CRP*
- *Low fibrinogen, coagulation disorder*
- *High ferritin and triglycerides*
- *Elevated transaminases, LDH*
- *Elevated sIL2R*

macrophage activation syndrome and anakinra

Whole-Exome Sequencing Reveals Mutations in Genes Linked to Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome in Fatal Cases of H1N1 Influenza

Grant S. Schulert,[1] Mingce Zhang,[3] Ndate Fall,[1] Ammar Husami,[2] Diane Kissell,[2] Andrew Hanosh,[4] Kejian Zhang,[2] Kristina Davis,[4] Jeffrey M. Jentzen,[4] Lena Napolitano,[5] Javed Siddiqui,[4,7] Lauren B. Smith,[4] Paul W. Harms,[4,6,7] Alexei A. Grom,[1] and Randy Q. Cron[3]

Therapeutic Role of Anakinra, an Interleukin-1 Receptor Antagonist, in the Management of Secondary Hemophagocytic Lymphohistiocytosis/ Sepsis/Multiple Organ Dysfunction/Macrophage Activating Syndrome in Critically Ill Children*

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This session

10:50-11:10 **Stroke in TB Meningitis: Path-Physiology, Clinical and Management Issues**
Usha Kant Misra (Sanjay Gandhi Postgraduate Institute of Medical Sciences)

11:10-11:30 **Host Genotypes, Inflammatory Response and Outcome of TBM; Vietnam Cohort**
Nguyen Thuy Thuong Thuong (Oxford University Research Unit, Ho Chi Minh City)

11:30-11:50 **Host Inflammatory Phenotype and Outcome TBM Indonesia**
Arjan van Laarhoven (Radboud University Medical Center)

Afterwards? Or sometime today / tomorrow

Cerebral tryptophan metabolism is critical in TBM