Βιολογικοί Παράγοντες και Λοιμώξεις

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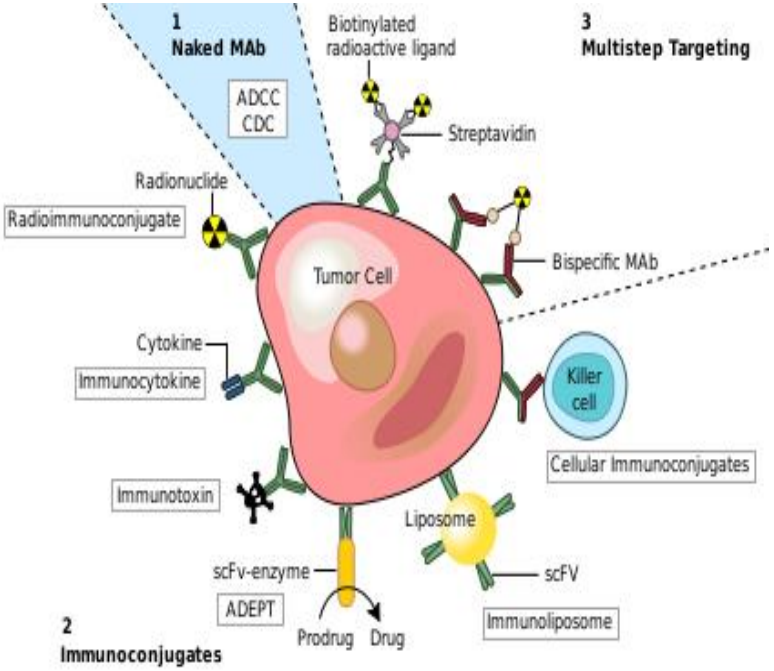
ΑΤΤΙΚΟΝ

Βιολογικοί Παράγοντες και Λοιμώξεις
Monoclonal antibodies (mAb or moAb)

- ✓ Monospecific antibodies
- ✓ Made by identical immune cells that are all clones of a unique parent cell
- ✓ Typically made by fusing myeloma cells with the spleen cells
- ✓ Recent advances have allowed the use of
  - rabbit B-cells to form a rabbit hybridoma
  - viruses or yeasts to create recombinant monoclonal antibodies



Marks JD et al, J Mol Biol 1991;222 (3): 581–597, Carmen S et al , Brief Funct Genomic Proteomic 2002; 1 (2): 189–203

Βιολογικοί Παράγοντες και Λοιμώξεις
Monoclonal antibodies (mAb or moAb)

Biological agent	Mechanism of action
Infliximab, Adalimumab Etanercept Ustekinumab, Briakinumab	Anti-TNF Neutralizes TNF Anti-IL-12/IL-23 (p40 subunit)
Infliximab, Adalimumab	Anti-TNF
Infliximab, Adalimumab	Anti-TNF
Omalizumab Mepolizumab	Anti-IgE Anti-IL-5
Teplizumab, Otelixizumab	Non-activating anti-CD3
Anakinra	Recombinant IL-1 receptor antagonist
Interferon β Natalizumab Rituximab Alemtuzumab	Immunoregulatory Anti-α4 integrin B-cell depletion (anti-CD20) Lymphocyte depletion (anti-CD52)

Βιολογικοί Παράγοντες και Λοιμώξεις
Monoclonal antibodies (mAb or moAb)

- Have changed the outcome of
  - rheumatoid arthritis and lymphoma
- mAbs → interaction with an antigen of immune and hematologic target leading to
  - blockade or reduction of effector cell function
  - depletion of B or T lymphocytes
  - inhibition of key intracellular and
  - cytokine interations

Uetwiller F et al, mABs 2011;3(5):1-6

Βιολογικοί Παράγοντες και Λοιμώξεις
Monoclonal antibodies (mAb or moAb)

- ✓ Increasingly used
- ✓ Therapeutic option for otherwise refractory non- rheumatic disease
- ✓ Provide proof-of-concept for proposed mechanisms of immunopathology

Bell G et al, Nature Reviews Rheumatology 2011;7:507-16,
Harrison, M. J. et al Ann. Rheum. Dis. 68, 209–215 (2009).

Βιολογικοί Παράγοντες και Λοιμώξεις

mAbs για μη ρευματοειδείς νόσους

Disease	Biological agent
Psoriasis	Infliximab, Adalimumab, Etanercept, Ustekinumab, Briakinumab
Inflammatory bowel disease	Infliximab, Adalimumab
Uveitis	Infliximab, Adalimumab
Asthma	Omalizumab , Mepolizumab
Type 1 diabetes mellitus	Teplizumab, Otelixizumab
Type 2 diabetes mellitus	Anakinra
Multiple sclerosis	Interferon-β, Natalizumab, Rituximab Alemtuzumab

Βιολογικοί Παράγοντες και Λοιμώξεις
mAbs – Παράδοξα φαινόμενα

- ✓ Worsening of heart failure
- ✓ Occasional induction of psoriasis
- ✓ Uveitis during tumor necrosis factor blockade

Bell G et al, Nature Reviews Rheumatology 2011;7:507-16, Harrison, M. J. et al Ann. Rheum. Dis. 68, 209–215 (2009).

Βιολογικοί Παράγοντες και Λοιμώξεις
Λοιμώξεις

- Deleterious and costly
- Intensity of immune downregulation
- Monitoring mediators of innate and adaptive immune responses
  - abnormalities of memory B-cell distribution poor outcome in common variable immunodeficiency
  - high percentage of activated CD8+/CD38+ T cells

    independent predictor of poor outcome in HIV infection

Βιολογικοί Παράγοντες και Λοιμώξεις
Alemtuzumab (Anti-CD52)

- Humanized mAb (IgG1kappa) , trade name MABCAMPATH®
- Specific for CD52 (21-28 kDa glycoprotein)
- Targets normal or pathologic mononuclear cells without affecting progenitor cells
  - Increase regulatory cells
  - Induce regulatory T-cell differntiation
  - Inhibit T-cell transmigration

Its activity is related with

- Antibody – dependent cell mediated toxicity (ADCC)
- Complement - toxicity
- Apoptosis induction

→

- Neutropenia
- Reduction
  - CD4, CD8 T cells, B and NK cells

Nücklel H et al. Eur J Pharmacol 2005; 514:21 -24

Βιολογικοί Παράγοντες και Λοιμώξεις
Λοιμώξεις και Alemtuzumab (Anti-CD52)

- Opportunistic infections
  - *Pneumocystis jirovecii*
  - CMV (10—15%)
- Pulmonary infections
  - in refractory lymphocytic leukemia
- Septicemia

Keep in mind
- the non opportunistic infections

ACTION
- mAb discontinuation
- PCR every week for CMV
- Cultures

TREATMENT
According to the findings

Osterborg A et al. Semin Oncol 2006;33:29-35, Osterborg A et al, Leukemia 2009;23:1980-8

Βιολογικοί Παράγοντες και Λοιμώξεις
Rituximab (Anti-CD20)

Humanized mAb (IgG1) , trade name RITUXAN® , MABTHERA®

Mainly used in oncology

Specific for CD20 expressed on normal and abnormal B cells

- Increase regulatory cells
- Induce regulatory T-cell differentiation
- Inhibit T-cell transmigration

Its activity is related with

- Antibody – dependent cell mediated toxicity (ADCC)
- Complement - toxicity
- Apoptosis induction

- Neutropenia
- Reduction
  - CD4, CD8 T cells, B and NK cells

Nücklel H et al. Eur J Pharmacol 2005; 514:21 -24

Βιολογικοί Παράγοντες και Λοιμώξεις

Rituximab (Anti-CD20) και Λοιμώξεις

- Low incidence
- Increased rates in
  - HIV pts ($CD4^+ < 50/\mu l$)
  - pts with immunosuppressive agents
- Opportunistic infections
  - mainly viral infections (CMV, parvovirus BK, JC, enterovirus)
- Reactivation of hepatitis B (HBV)

Keep in mind
- the non opportunistic infections

ACTION
- mAb discontinuation ????
- PCR for virus
- Cultures

TREATMENT
- According to the findings
- Prophylaxis
- Lamivudine (HBV) ?

Kamar N et al , Am J Transplant 2010;10:89-98, Aksoy S et al, Leuk Lymphoma 2007; 48:1307-12, Dervite I et al, NEJM 2001;344:68-9

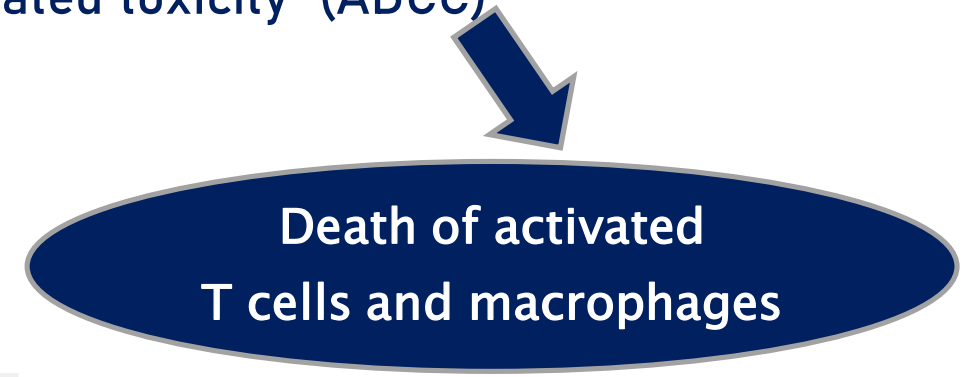
Βιολογικοί Παράγοντες και Λοιμώξεις
Anti-TNF mAbs

Infliximab, Adalimumab Etanercept

Infliximab (REMICADE®) , adalimumab (HUMIRA)® : neutralize TNF

Etanercept (ENBREL®) : fusion protein (human IgG1 Fc fragment + extracellular portion of the TNFα receptor

Antibody – dependent cell mediated toxicity (ADCC)



Di Sabatinio A et al, Gut 2004;53:70-7

Βιολογικοί Παράγοντες και Λοιμώξεις
Anti-TNF και Λοιμώξεις

- Tuberculosis
- Atypical *mycobacteria* infections
- Infections due to
  - *Listeria, Nocardia,* Coccidiosis, streptococci
- Some cases with fungal infections
- Usually they are apparent in the first 6 months of the treatment
- Viral infections
- HBV reactivation

Before treatment
- screening for TBC
- CxR, tuberculin and/or INF-Elispot test

After treatment in case of infection
- mAb discontinuation
- PCR for virus / TBC
- Cultures

Treatment according to the type of infection
- Prophylactic Lamivudine for HBV

Kiim YJ et al, J Rheumatology 2010;37:346-50, British Soc Rheumatology . Rheumatology 2011;50:124-31

Βιολογικοί Παράγοντες και Λοιμώξεις
Anti-Integrin και Λοιμώξεις

Anti-VLA-4 (Natalizumab) και Anti-CD11a (Efalizumab)

Natalizumab (TYSABRI®)

- humanized IgG4 targeting the α4 chain of the α4β2 integrin (VLA-4)
- JC infection ➔ progressive multifocal leucoencephalopathy
- Is contraidicated in cases of HIV pts
- Leucopenia with immunosuppressive agents

Efalizumab (RAPTIVA®)

- humanized mAb targeting the CD11a of LFA1 (CD11a/CD18)
- Was withdrawn in 2009

Berger JR, Drug Saf 2010;33:969-83, Carson KR et al, Lancet Oncol 2009;10:816-24

Βιολογικοί Παράγοντες και Λοιμώξεις
CTLA4-Ig : Abatacept, Belatacept

Abatacept (ORENCIA®)

- Is a fusion protein composed of an immunoglobulin Fc fused to the extracellular domain of CTLAA4 (CD80/CD86)

Belatacept

- in phase 2 (fusion protein)

- No- opportunistic infections reported
- Severe common infections are common
- Anecdotal reports
  - sporadic cases of septic arthritis, cellulitis etc.

Snanudi R et al, Drugs 2010;70:2121-31, Robak T et al, Bio Drugs 2011;25:13-25

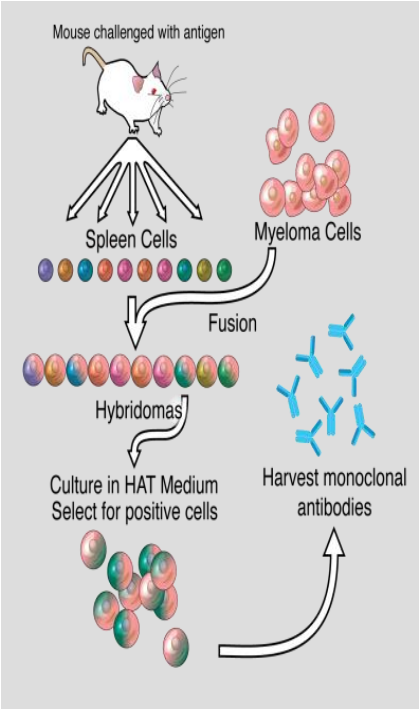
Βιολογικοί Παράγοντες και Λοιμώξεις
Eculizumab

Ecuilizimab, trade name Soliris®

Against the complement protein C5

Recombinant humanized monoclonal $IgG_{2/4}$ antibody

- ✓Congenital atypical hemolytic uremic syndrome
- ✓Severe shiga-toxin associated hemolytic uremic syndrome
  - enterohemorrhagic *E. coli* in Germany
- ✓Cold agglutinin disease
- ✓Kidney transplants



Hillmen P et al, NEJM 2006; 355 (12): 1233–1243
Lapeyraque et al Eculizumab in Severe Shiga-Toxin–Associated HUS". N Engl J Med 2011;364: 2561–2563.

Βιολογικοί Παράγοντες και Λοιμώξεις
Eculizumab και Λοιμώξεις

Eculizumab
- inhibits complement activation and therefore makes patients vulnerable to infection with encapsulated organisms

Serious meningococcus infections

Before treatment
- Meningococcal vaccination at least 2 weeks prior to receiving eculizumamb

After treatment in case of infection
- mAb discontinuation

Treatment according to the type of infection

Dmytrijuk A et al, The Oncologist 2008;13 (9): 993–1000

Βιολογικοί Παράγοντες και Λοιμώξεις
Βιοδείκτες για την ανίχνευση κινδύνου λοιμώξεων

Immunological biomarkers used before
and after immunosuppressive or biologic therapies

- Neutrophil count
- *Mycobacterium tuberculosis* hypersensitivity *tests*
- Serological cytomegalovirus (CMV) status donors and recipients

Βιολογικοί Παράγοντες και Λοιμώξεις
Φυματίωση και mABs

Tableau I.

Médicaments immunosuppresseurs potentiellement pourvoyeurs de tuberculose (TB).

Classification Mode d'action	Médicaments	Indications	Risque théorique de TB
Lympho-ablatifs – Destruction du tissu lymphoïde – **plus spécifiques du lymphocyte T (LT)**	Alkylants... cyclophosphamide OKT3, Fludarabine	Chimiothérapie des cancers et hémopathies Maladies systémiques	±
Antimétabolites – inhibe la synthèse des purines, **pyrimidines** – Blocage de l'expansion LT activé	Mycophénolate mofétil, Azathioprine **Méthotrexate, Léflunomide**	Prévention du rejet (immunité LT) Maladies systémiques	+
Antiprolifèrants – Contrôle l'entrée en phase S du cycle cellulaire par fixation au récepteur à la rapamycine	Sirolimus Everolimus	Prévention du rejet	+
Anticalcineurine – Inhibe le premier signal d'activation du LT	Cyclosporine A, FK 506 (Tacrolimus)	Prévention du rejet	+
Corticoïdes – Inhibe toute la réaction immuno-inflammatoire	Prednisone, méthylprednisolone	Maladies systémiques Prévention du rejet de greffe Oncologie, asthme, PHS, FID...	++
Agents anti-TNFα – Inhibent la principale cytokine pro-inflammatoire	Infliximab Adalimumab Etanercept	Maladies systémiques	+++

PHS : Pneumopathie d'hypersensibilité ; FID : Fibrose interstitielle diffuse.

Tableau IV.

Incidence et risque relatif (*RR*) de tuberculose dans la polyarthrite rhumatoïde (PR) avant et après introduction des agents anti-TNF-α. Impact des recommandations.

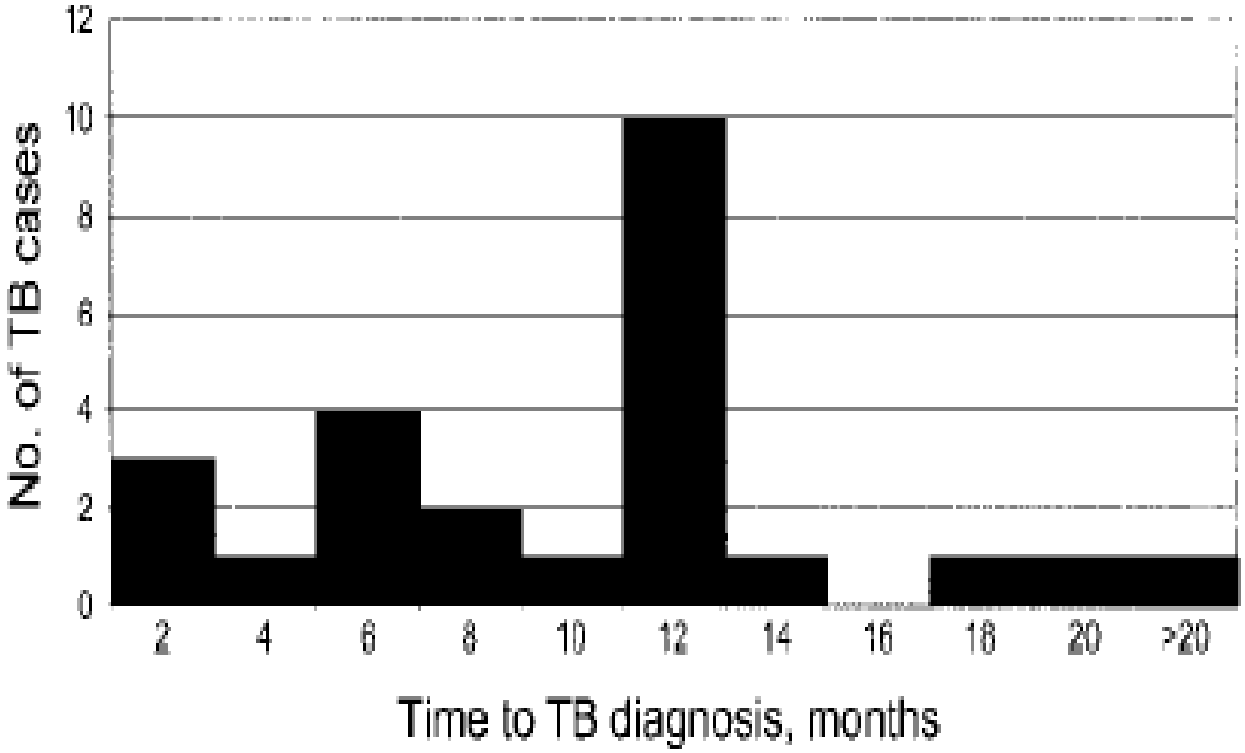
Incidence/100 000 et *RR* de tuberculose	USA Wolfe 2004 [38]	Espagne Gomez-Reino 2003 [39] Carmona 2005 [52]	Allemagne Perez 2004 [56]	Suède Askling 2005 [40]	Corée Séong 2007 [41]
Dans la population générale	6,2	25	17,5	4 -14*	67
RR	1	1	1		1
Dans la PR	6,2	110	?		257
RR		4,7	?	2	4
Dans la PR sous anti-TNFα	24,5	522	130	118	2300
RR cumulé	4	20 (4,7 x 5)	9	8(2 x 4)	36 (4 x 9)
Dans la PR sous anti-TNFα avec recommandations	6,2	117	15		
RR	1	4,7	1		
Efficacité	Prouvée	Prouvée		Prouvée	

**Incidence d'hospitalisation pour tuberculose.*

H. Lioté. Rev Mal Respir 2008 ; 25 : 1237-49

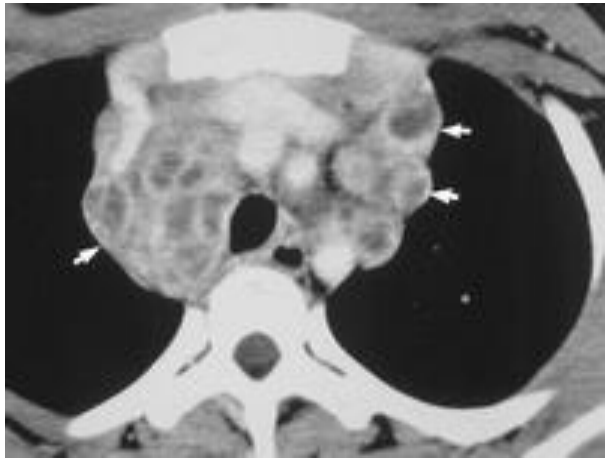
Βιολογικοί Παράγοντες και Λοιμώξεις

Φυματίωση μετά από Etanercept

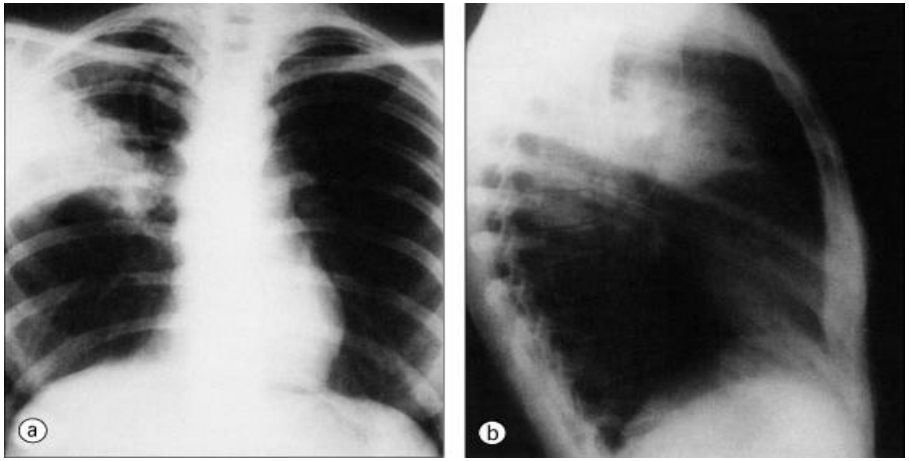


Mohan AK et al. Clin Infect Dis 2004; 39:295–9

TB σε ασθενείς με mAbs

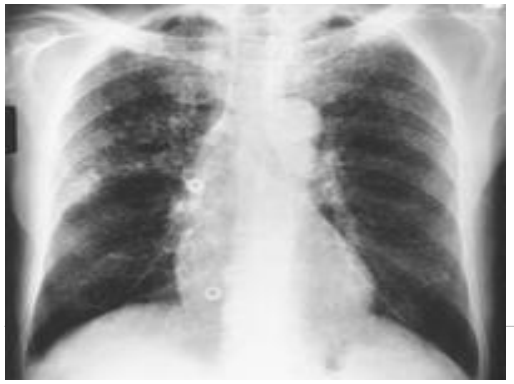


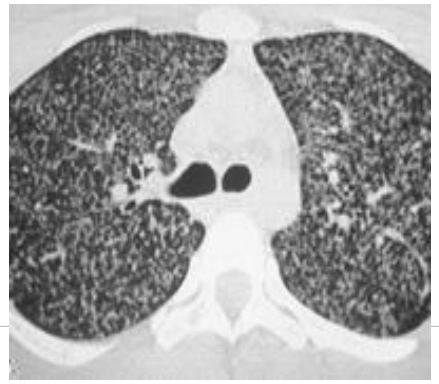
Mediastinal lymphadenitis



Tuberculous pneumonia

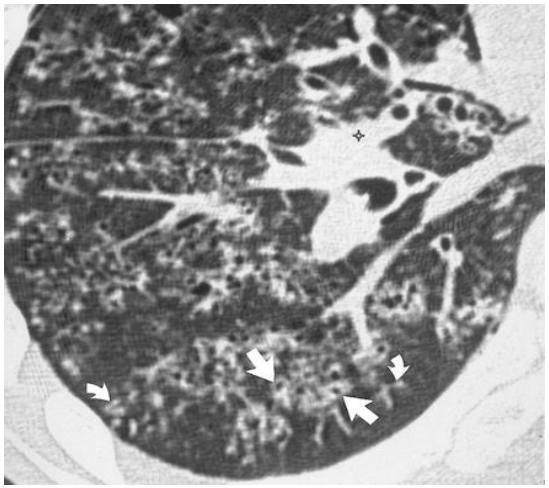
Courtesy of Dr W Lynn, Ealing Hospital, UK.



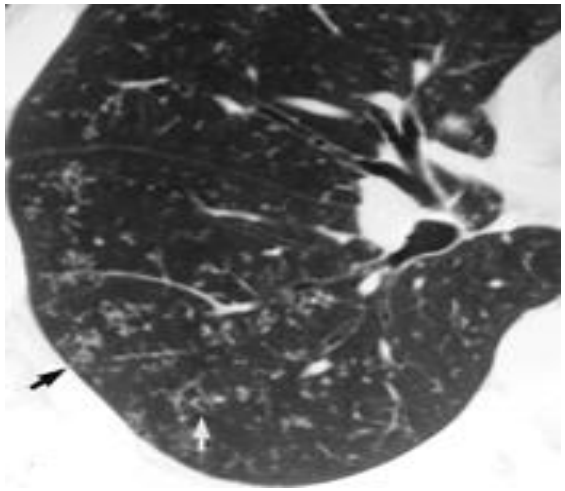


Miliary TBC

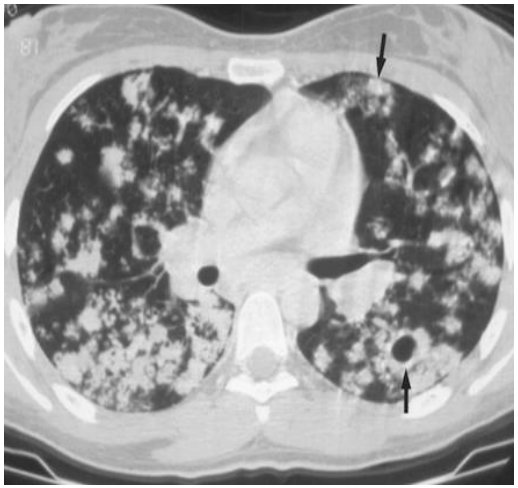
Ακτινολογικά ευρήματα



Tree-in-bud pattern

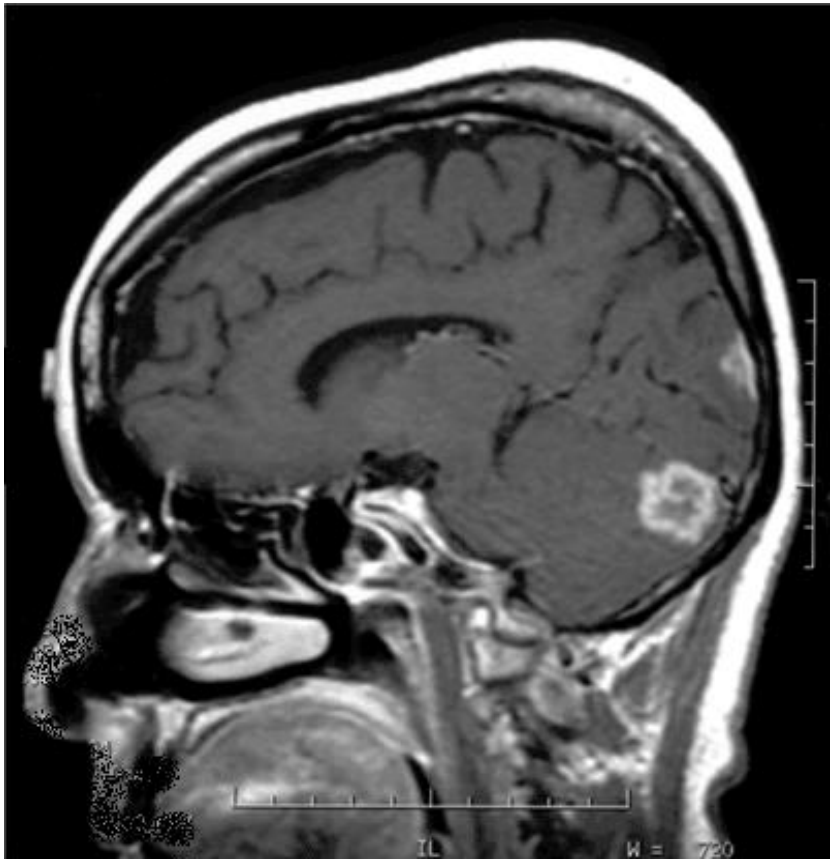


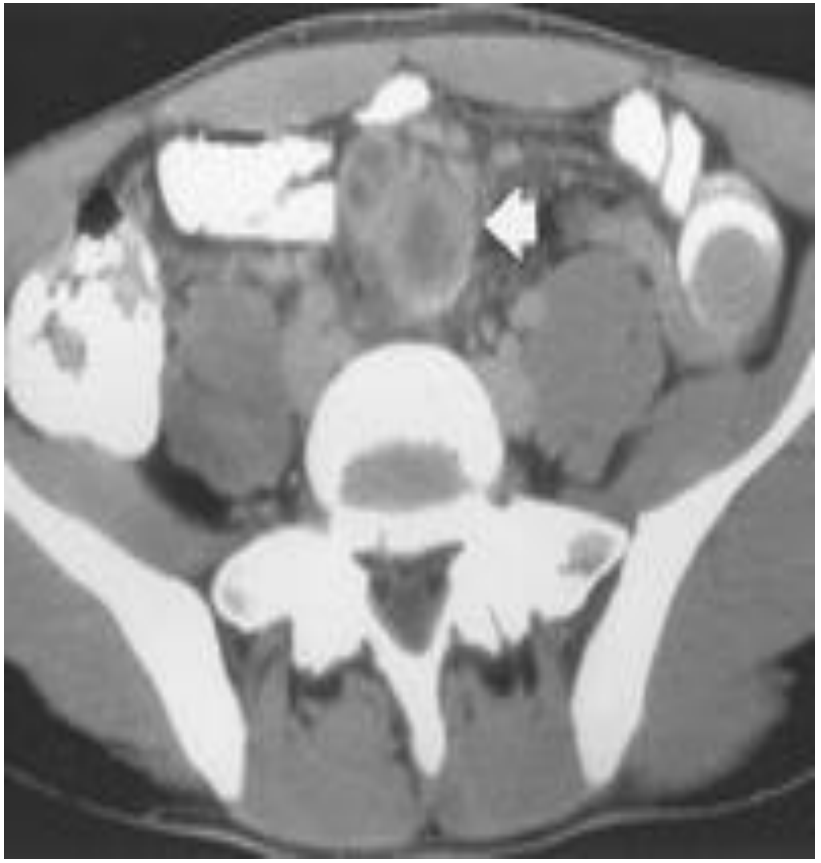
Multiple nodular lesions



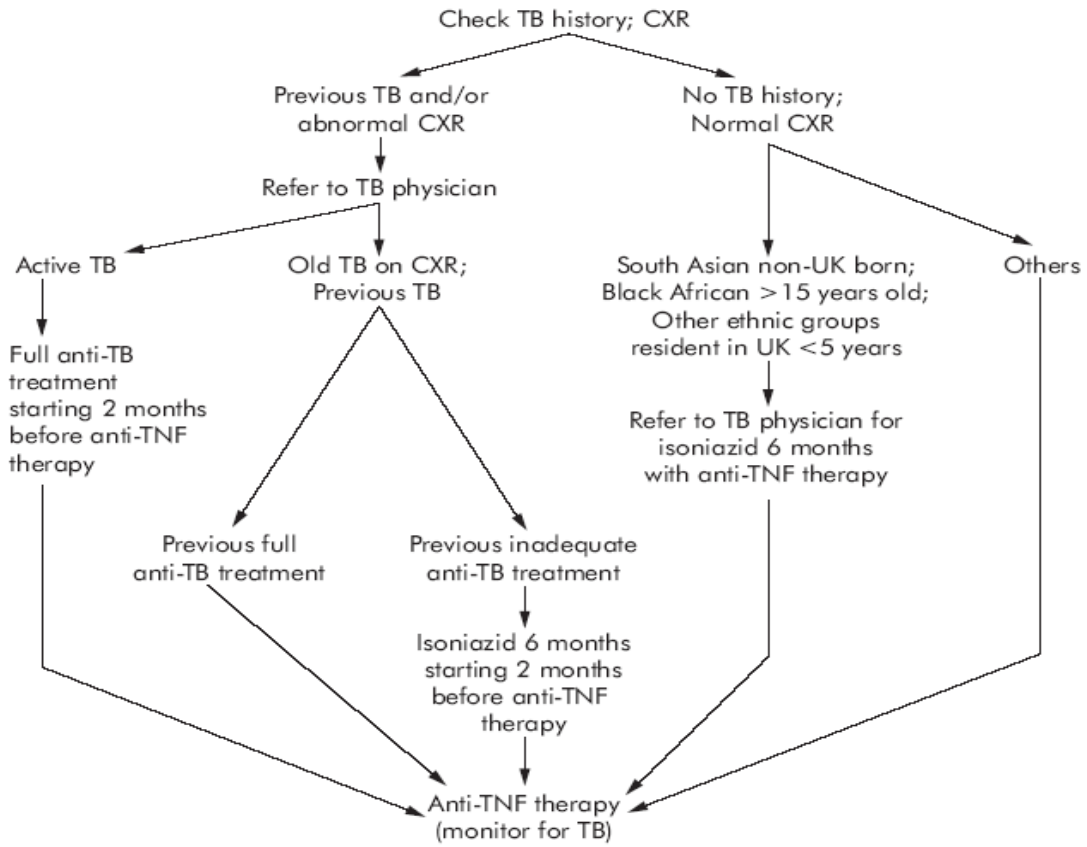
Intrabronchial dissemination

ΤΒ σε άλλα ανατομικά σημεία





Πρόληψη TB σε άλλα ανατομικά σημεία



Preventing TB in patients with Crohn's disease needing anti-TNF therapy

D S Rampton. Gut 2005;54:1360–1362.

Immune Reconstitution Inflammatory Syndrome (IRIS)

Paradoxical worsening of clinical status

- related to recovery of the immune system after immunosuppression leading to host inflammatory responses to previously recognized or subclinical infections

Immune reconstitution

- may also result from an inflammatory or Immune response to cancer or self-antigens

IRIS is synonymous

- Immune restoration disease or Immune reconstitution syndrome

Other authors have expanded the spectrum of IRS to include a clinical deterioration induced by reduction or withdrawal of immunosuppressive agents in HIV (–) individuals.

Crothers C et al, Respirology 2009;14:486-94

Clinical illness consistent with IRIS in non HIV-patients

MAC infection
Cryptococcosis
Herpes simplex, Herpes zoster
Hepatitis C and B virus infection
CMV infection
Kaposi sarcoma
Sarcoidosis
Graves disease
Hashimoto thyroiditis
Drug-induced hypersensitivitis syndrome

Types of IRIS

Early IRIS = days-3 months
Late IRIS = months after treatment

-'Unmasking' form = due to a previously undiagnosed subclinical infection at the time that therapy is initiated

- 'Paradoxical' form = related to a previously known opportunistic pathogen that was initially responding to therapy

Both types require an adequate immunological and virological response to the treatment

Conclusions

- Treatment with mAbs is related with infections
  - Opportunistic, non- opportunistic
  - Bacterial, Viral, TBC
- Early recognition and treatmnet is important
  - PCR, cultures etc
- Possible discontinuation of mAbs
- Vaccination prior to start mAbs treatment