ΚΥΠΡΙΑΚΗ ΕΤΑΙΡΕΙΑ ΠΑΘΟΛΟΓΙΑΣ

CYPRUS SOCIETY OF INTERNAL MEDICINE

FEVER IN A MIDDLE-AGED HEALTH PROFESSIONAL WOMAN WHAT LIES BENEATH…

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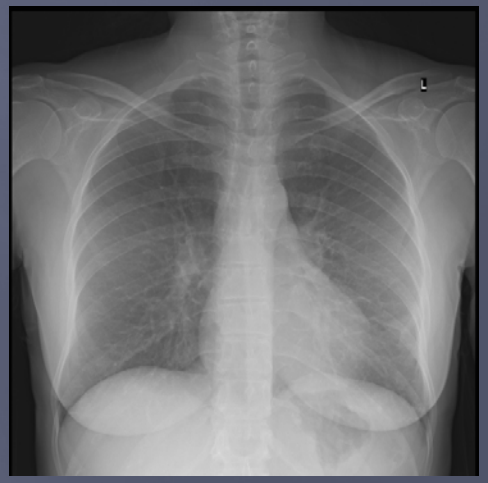
Initial presentation

- Presenting condition
  - 45-year old female
  - Fever (up to 39 degrees Celcius) with rigor over the past 2 weeks
  - Headache
  - Sore throat / tenderness and pain in anterior neck
  - Non-productive Cough
  - Myalgia - Arthralgia
  - Fatigue



- Personal history
  - Breast silicone implants (for cosmetic reasons) in 2006
  - Occupation: nurse in Nicosia General Hospital
  - Potential exposure to rodents
- Physical examination
  - Cardiac examination: regular sinus rhythm without additional heart sounds
  - Respiratory examination: Breath sounds normal in both lungs
  - Abdomen: soft and non-tender with normal bowel sounds
  - No organomegaly or lymphadenopathy
  - Skin examination: unremarkable
  - No major findings in neurological and sensory examination
- CXR, ECG normal

Laboratory tests on admission:

- **WBC 12300 (N 85.6%,** L 6.6%, M 7%, E 0.6%)
- **Hgb 10.9 g/dl, MCV 76**, PLT 300,000)

- Urea, creatinine, electrolytes normal
- ALT 151, AST 97

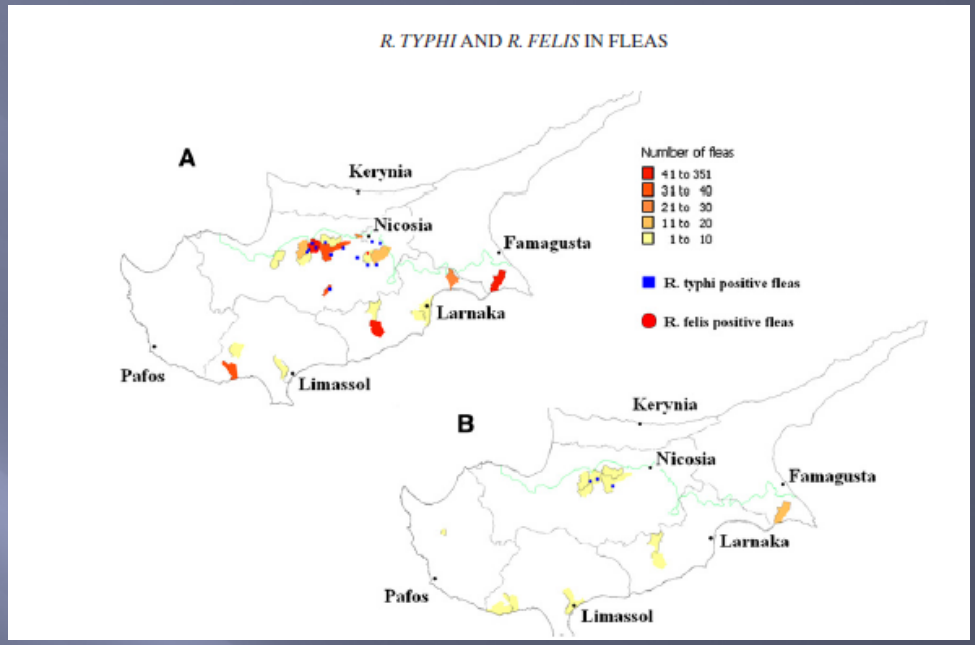
- MSU normal

What's the most likely diagnosis?

Our Differential diagnosis

- Rickettsial infection?
- Leptospirosis?
- Viral infection???

Rickettsiae in Cyprus



The endemic nature of infections by *Rickettsia spp* and *Coxiella burnetii* has been well documented in Cyprus, with 20-25 cases reported via the WHO compulsory notification system annually, which correspond to an incidence rate of about 2.5 new cases /100.000 inhabitants every year. Thus, endemic typhus, q fever and Mediterranean spotted fever should always be considered in cases of prolonged fever of indeterminate etiology, especially if this is accompanied by a compatible medical history and clinical examination. Diagnostic confirmation may be provided via serological or molecular testing, with the latter technique offering higher specificity and sensitivity but also demanding a considerably higher cost. Despite the significant impact of rickettsial disease in terms of public health, limited data is available on their clinical spectrum or their responsiveness to initial doxycycline therapy (standard of care).

Workup

- Laboratory exams (Weil-Felix Reaction, semi-quantitative ELISA for R. typhi, Leptospira and C. burnetti Abs) to confirm rickettsial infection
- Extended viral serology for acute infection
- Inflammatory markers persistently increased: hs-CRP 8.86, ESR 34, PCT 0.23
- Empirical treatment with doxycycline 100 mg bd

Fever did not respond to doxycycline after 5 days…

Alternative diagnosis???

➢Bacterial infection???

- •Blood culture sets for aerobic and anaerobic bacteria
- •Empirical broad-spectrum antibiotic regimen

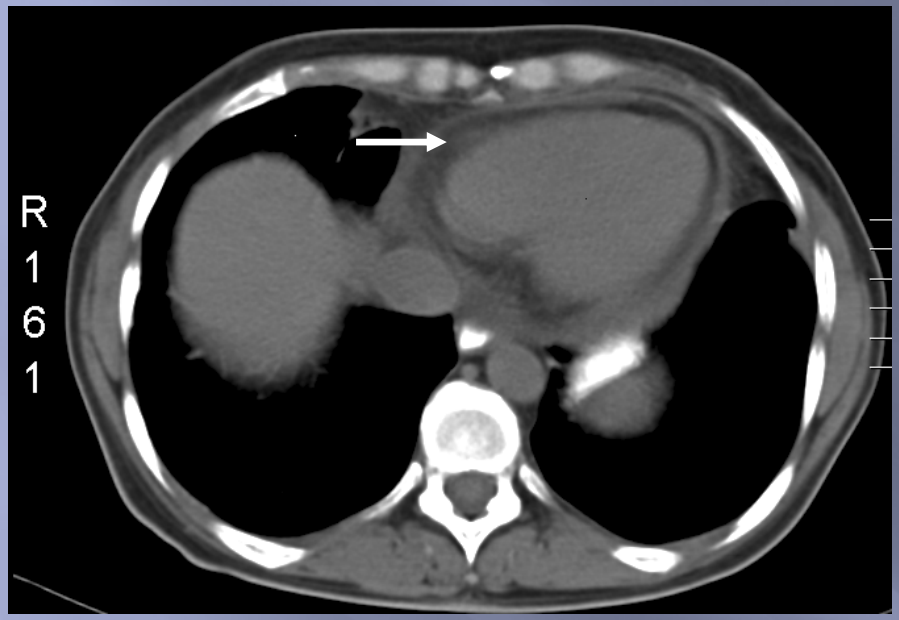
Further workup

- Coxiella phase I and II, R. typhi, Leptospira, Weil Felix Reaction (-)
- Blood cultures negative
- Legionella *pneumophila* serogroup 1 antigen and Strept. *pneumoniae* antigen in urine not detected
- Extended viral screening negative

Fever > 38.3
Duration > 3 weeks → **FUO**
No diagnosis after 1 week of investigation

- Autoimmunity serological screening, antithyroid antibodies
- US of neck, thyroid gland and abdomen (-)
- CT chest: pericardial fluid 1 cm, mediastinum nodules 11 mm
- Echo: pericardial effusion 0.5 cm
- Laryngoscopy, otoscopy: unremarkable findings
- TST and Bronchoscopy (BAL, b Koch, cytology) (-)
- LP: normal
- Ophthalmological examination, fundoscopy: no major findings
- Liver biopsy…

- Breast mammography (-)
- Gastroscopy: gastritis, hiatus hernia. Biopsy and gastric fluid for b Koch (-)
- Colonoscopy: normal.
- Bone marrow biopsy (-)
- Protein electrophoresis: normal
- Gallium scan (-)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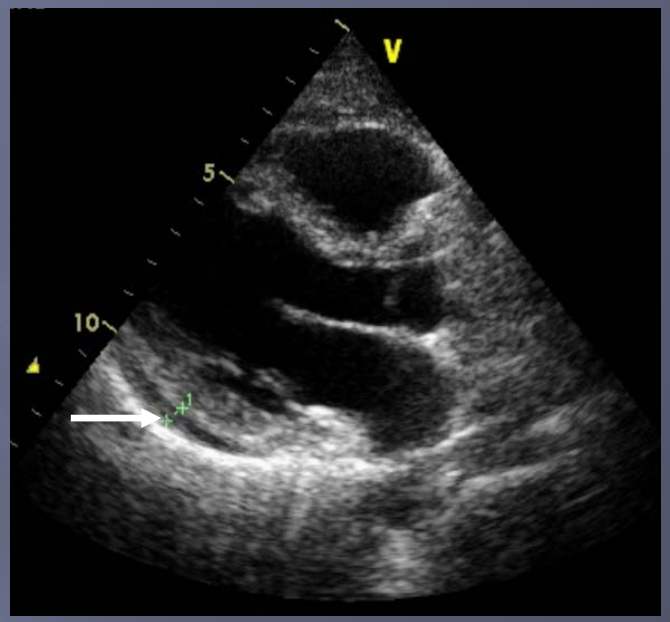
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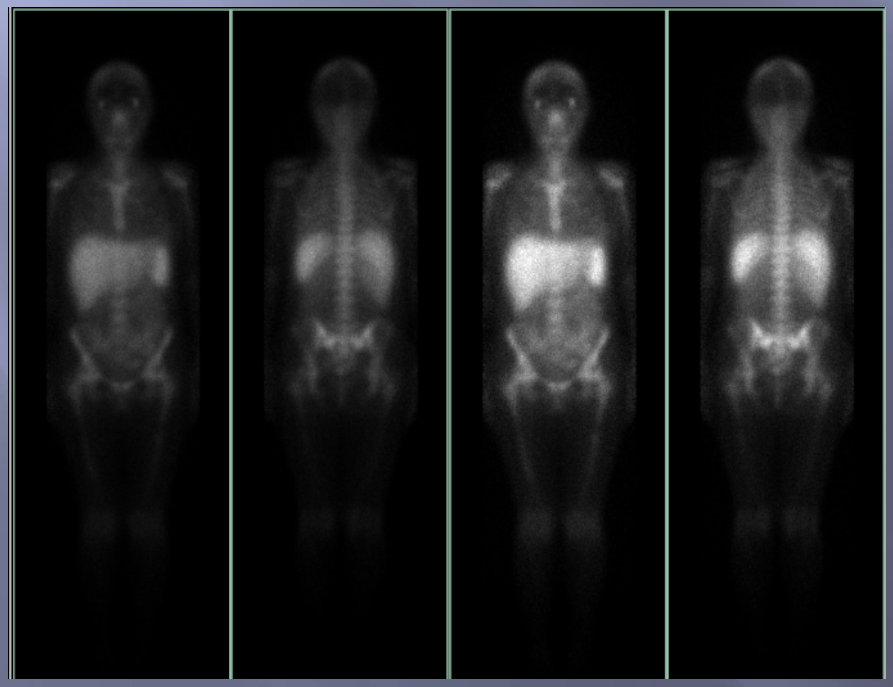
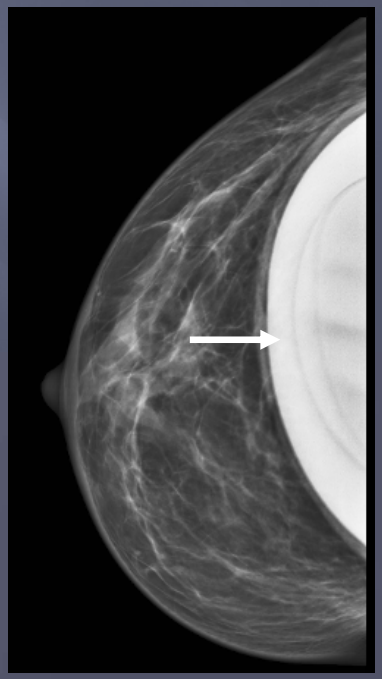




New data

Clinical Findings:

- Pain, swelling, redness of the left ankle
- Salmon pink rash over the trunk and lower extremities
- Dyspnea with fine crackles - pericarditis

Laboratory Findings:

- Ferritin 5400
- ANA, anti-ds DNA, RF, anti-CCP, C3, C4, ANCA: negative

Differential diagnosis?

➢Still's disease???

Yamaguchi criteria for adult Still's disease

- The Yamaguchi criteria require the presence of five features, with at least two being major diagnostic criteria.

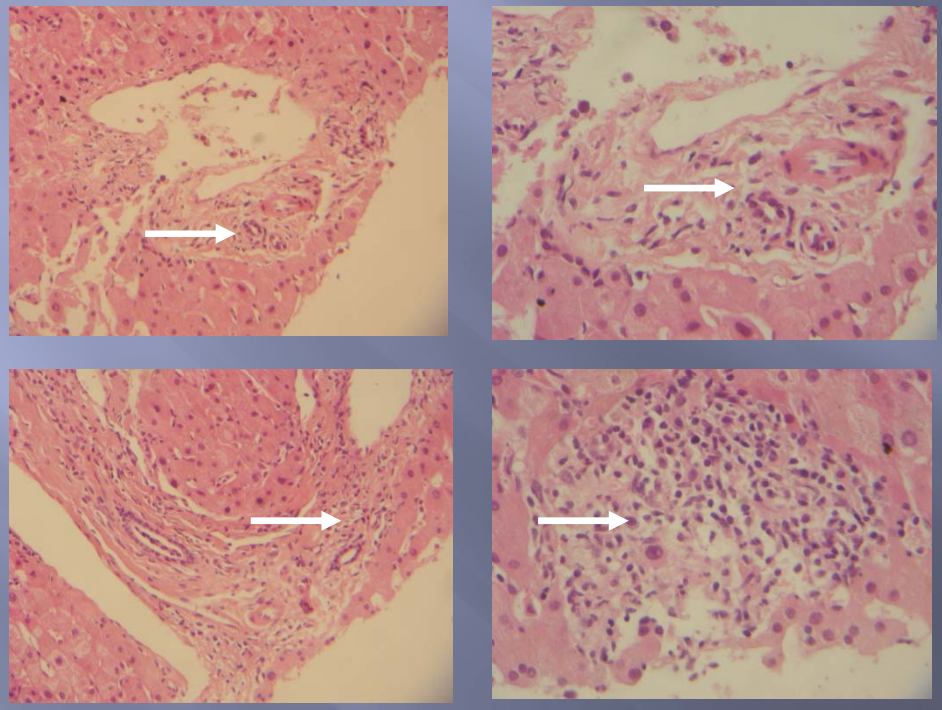
- **Major Yamaguchi criteria:**
  - Fever of at least 39°C lasting at least one week
  - Arthralgias or arthritis lasting two weeks or longer
  - A non-pruritic macular or maculo-papular skin rash that is salmon-colored in appearance and usually found over the trunk or extremities during febrile episodes
  - Leukocytosis (10,000/microL or greater), with at least 80 percent granulocytes
- **M inor Yamaguchi criteria:**
  - Sore throat
  - Lymphadenopathy
  - Hepatomegaly or splenomegaly
  - Abnormal liver function studies, particularly elevations in aspartate and alanine aminotransferase and lactate dehydrogenase concentrations
  - Negative tests for antinuclear antibody and rheumatoid factor

- **Exclusions** The presence of any infection, malignancy, or other rheumatic disorder known to mimic ASD in its clinical features precludes the diagnosis of ASD

Liver biopsy

Core biopsy of liver, segmental staining, H-E

Findings of chronic hepatitis and sclerotic-hyaline nodules secondary to foreign body exposure (silicone-induced hepatotoxicity):



1. Increase of collagenous / fibrous stroma with areas of hyalinization. 100x

2. 200x magnification of image 1, showing extensive hyalinization of pericholangiolar stroma

3. Portal triad and central vein segment of hepatic lobule with extensive inflammatory infiltration, 100x

4. 200x magnified view of pericholangiolar area showing inflammatory infiltration by lymphocytes, plasmacells and few eosinophilic leucocytes – possible foreign body granuloma

Is there an association between breast implants and autoimmune / connective tissue disease???

Anti-silicone antibodies testing ordered via reference laboratory in UK

"Final" diagnosis?

- Anti-silicone antibodies: positive

Silicone-induced Still-like inflammatory syndrome

- Treatment
  - Prednisone 40 mg daily
  - Colchicine
  - Breast implants removal

Follow up

- Regression of fever and all other symptoms under corticosteroid treatment
- On-going corticosteroid tapering
- Persistent regression after steroid discontinuation is necessary for final diagnosis
- Prolonged follow up for fever, ferritin, aminotransferases and inflammatory markers will be required


Thank you for your attention!!!
Cyprus

- References:
- Blasiak A. Still's disease in patient with silicone breast implants: case report. Polskie Arch 2008, 118:1-2
- Genovese MC. Fever, rash and arthritis in a woman with silicone gell breast implants. WJM 1997, 167 (3): 149-158
- Oliver DW. Anti-silicone antibodies and silicone containing breast implants. Br J Plast Surg 2000, 53(5): 410-414.