Clinico-pathological conference - 1

Ramon Pujol

ESIM

Saas Fee, 17th January 2012

Bellvitge Hospital

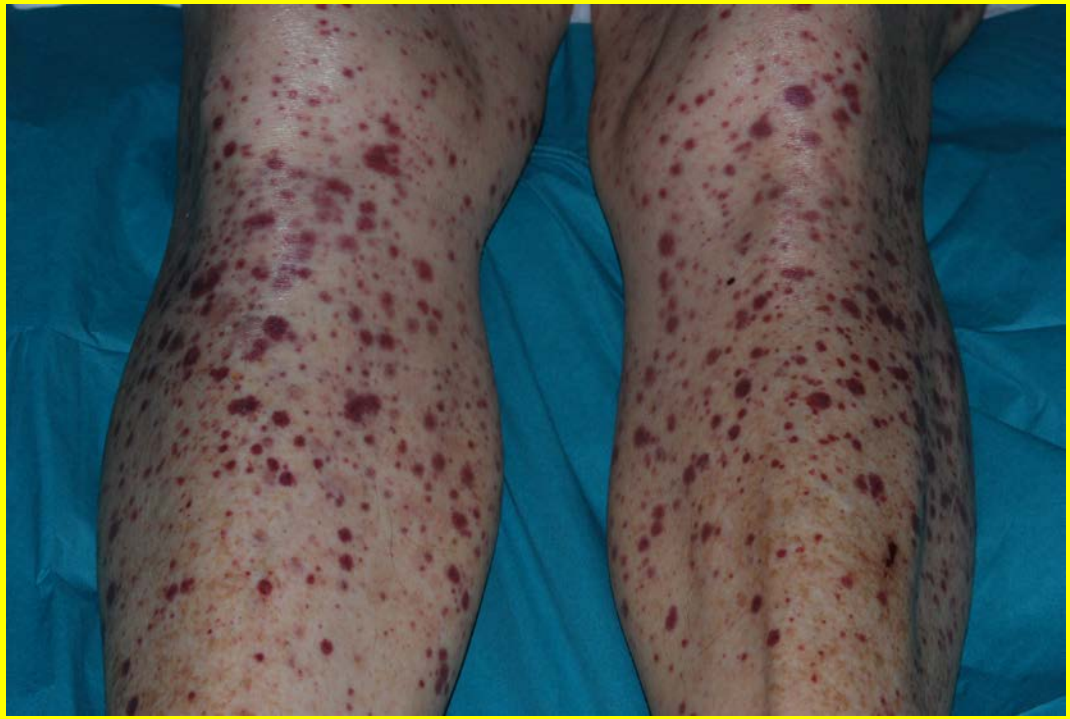
Institut Català de la Salut

Presentation of case

- Male, 70 y.
- HBP, last 10 y. Amlodipine & Doxazosin
- Diabetes, last 9 m. Metformin → Sitagliptin
- AV Block, 8 m. → VVI pacemaker
- COPD, GOLD I
- Colonoscopy, 3 m. → Multiple large polyps with high grade dysplasia. Subtotal removal.

Presentation of case. First admission, 22 nd July 2011

- Anorexia, 20 kg weight loss in 3 months, purpura and swelling of right leg.



Presentation of case
Physical examination

- Pulse 62, BP 149/63, temperature 36.4 º, satO_2 98%
- Positive findings:
  - Isolated soft lymphadenopathy in right groin
  - Dry crackles in low right lung
  - Swelling of right leg, purplish, and petechiae

Abnormal blood tests (increased, decreased)

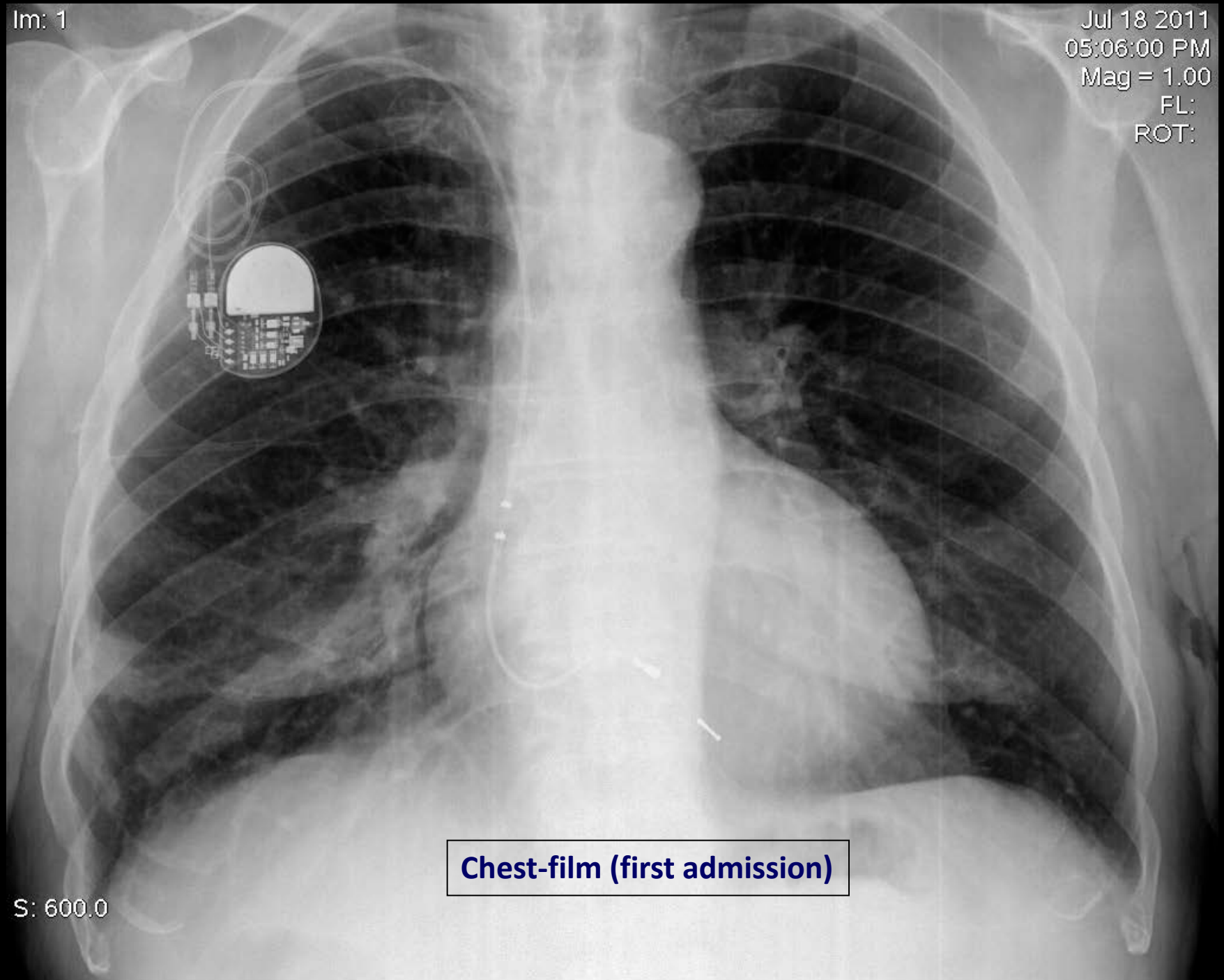
Blood lab test	July 22nd
Alkaline phosphatise, µkat/l	1.5
Gamma GT, µkat/l	1.4
Lactic-dehydrogenase, µkat/l	3.5
C-reactive protein, mg/l	54.6 *
ESR, mm	61 *
Albumin, g/l	33
Gamma globulin, %	33.2 *
Rheumatoid factor, u.i.	65.3 *
Iron, µmol/l	4
Blood count	
• Hemoglobin, g/l (MCV,fl; MCH,pg)	107 (85, 27)
• Hematocrit, %	32
• WBC count, x 10^9/l	10.7
• Neutrophil count, %	69
• Lymphocyte count, %	31
• Platelets, 10^9/l	210
Immunoglobulin G, mg/l	27,300 *
Immunoglobulin A, mg/l	5,650 *
Immunoglobulin M, mg/l	3,140 *
Complement C_4, mg/l	34 *
Complement CH50, mg/l	22 *
Beta-2 microglobulin, mg/l	3

- tumoral antigens
- B and C hepatitis antibodies
- HIV antibodies
- Stool cultures & parasites

Negative

*

*** highlights**



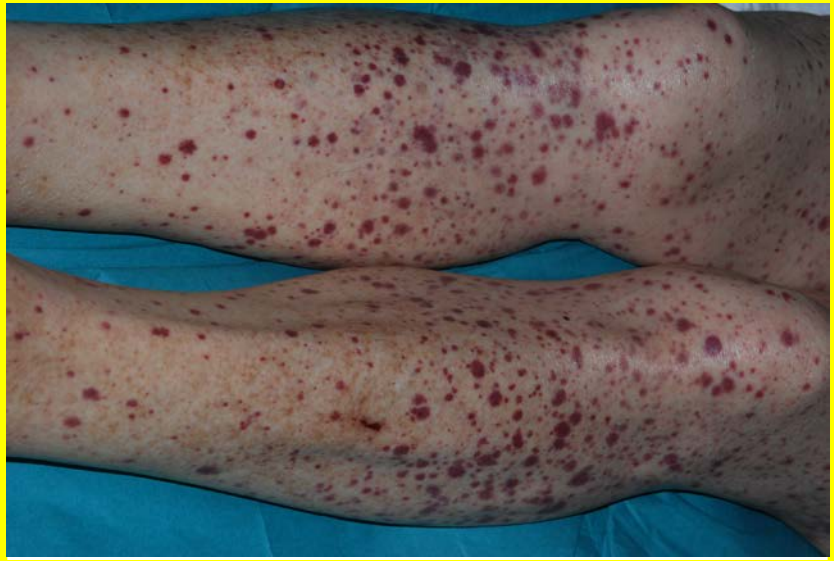
Chest-film (first admission)

Other tests

- CT-scan & PET-scan:
  - Emphysema
  - Hypermetabolic lesion in RLL (inflammatory *vs* infectious)
  - Hypermetabolic focus in colonic hepatic flexure
- FNAP lymphadenopathy: inflammatory
- Bone marrow: no leishmania or AFB
- PPD, 2 UT: 10 mm
- Right Temporal Artery Biopsy: No arteritis

Outpatient

- Lost additional 4 kgs
- New purpuric lesions (biopsy leukocytoclastic vasculitis)



Cryoglobulin POSITIVE
(monoclonal IgM λ,
polyclonal IgG)

New admission planned for treatment
The day before: fever with chills

Last admission, 6th September 2011

- Impaired general condition
- No new findings on physical examination
- Renal involvement
  - Proteinuria 1 gr/24 h., microscopic hematuria, renal failure
  - Worsening of anemia, RF, APR, nutritional markers.

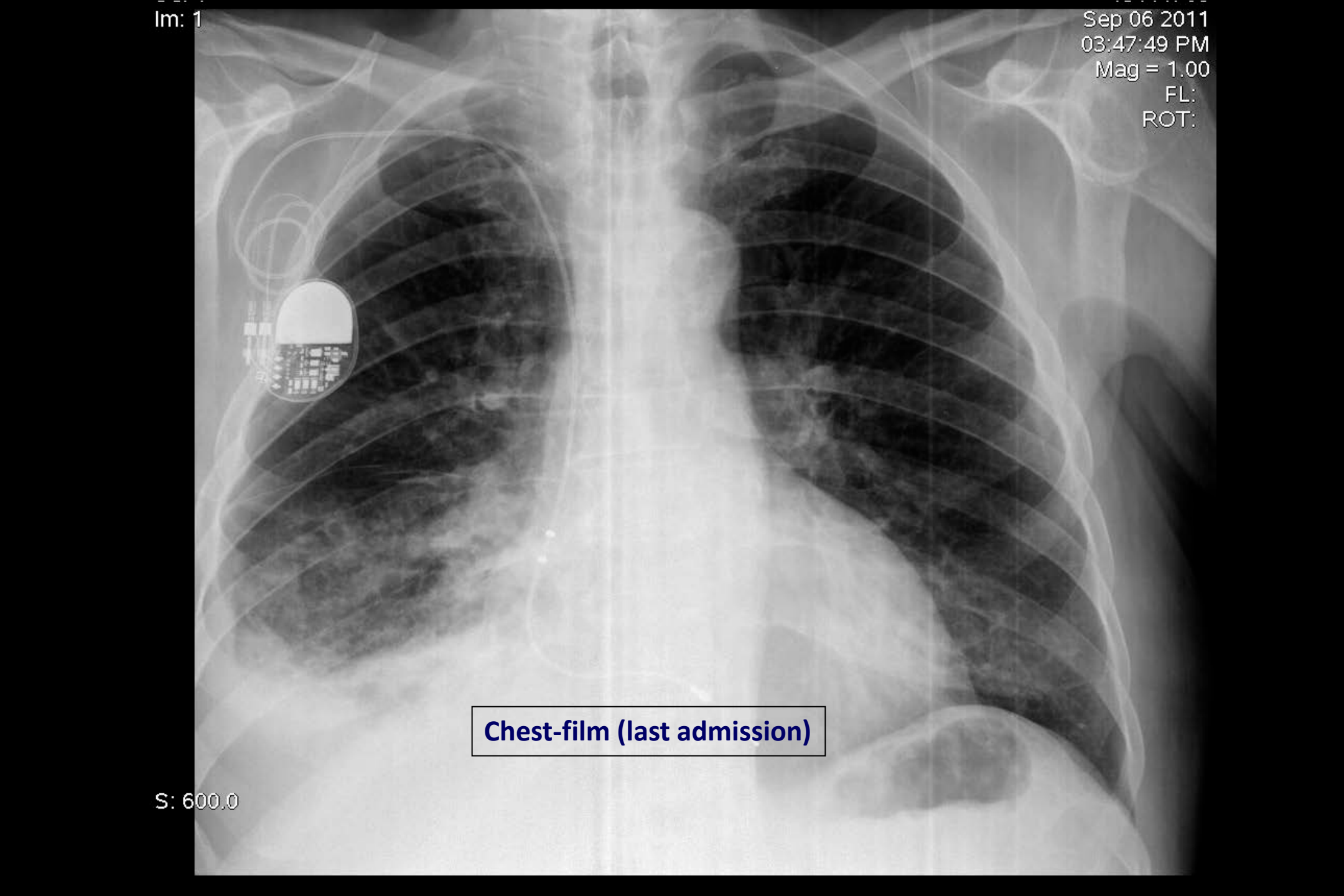
Abnormal blood tests (increased, decreased)

Blood lab test	September 6th
Alkaline phosphatise, µkat/l	2.2
Gamma GT, µkat/l	2.5
Lactic-dehydrogenase, µkat/l	3.7
C-reactive protein, mg/l	59.2
Albumin, g/l	24
Rheumatoid factor, u.i.	161.8
Iron, µmol/l	3
Blood count	
•Hemoglobin, g/l (MCV,fl; MCH,pg)	64 (80, 26)
•Hematocrit, %	20
•WBC count, x 10^9/l	12.9
•Neutrophil count, %	84
•Lymphocyte count, %	12
•Platelets, 10^9/l	263
Complement C_3, mg/l	414
Complement C_4, mg/l	61.1
Complement CH50, mg/l	61
Creatinine µmol/l	308
Uric acid, µmol/l	688
GFR, ml/min	18.2
Calcium, mmol/l	1.09
Reticulocytes, %	3.3

New abnormalities

Follow-up

- Bolus of methylprednisolone (0.5 gr/day) started
- At the beginning of second bolus: dyspnea, sweating, BP 220/120, satO_2 92% with FiO_2 50%.
- Transferred to Critical Care Unit.
- Improved after i.v. vasodilators, furosemide and morphine.
- **New results allowed a diagnosis……..**



Chest-film (last admission)

Our understanding

- **Main clue**, Mixed cryoglobulinemia (MC), cryoglobulinemic vasculitis (skin, kidney, lung ?)

Most frequent causes of MC *

• INFECTIOUS	Hepatitis C virus, Hepatitis B virus.....others
• AUTOIMMUNE	Sjögren's sd., SLE, RA……..others
• CANCER	B-cell lymphoma, multiple myeloma…others
• Other causes	Hepatic cirrhosis, cocaine abuse, ……others

**** Manuel Ramos-Casals et al. thelancet.com. August 24, 2011***

OK, but……..

- Confounding factor: NO B nor C hepatitis
- No advanced cancer or autoimmune disease found

- Main facts in the past history: colonic disease & AV block

The diagnosis !!

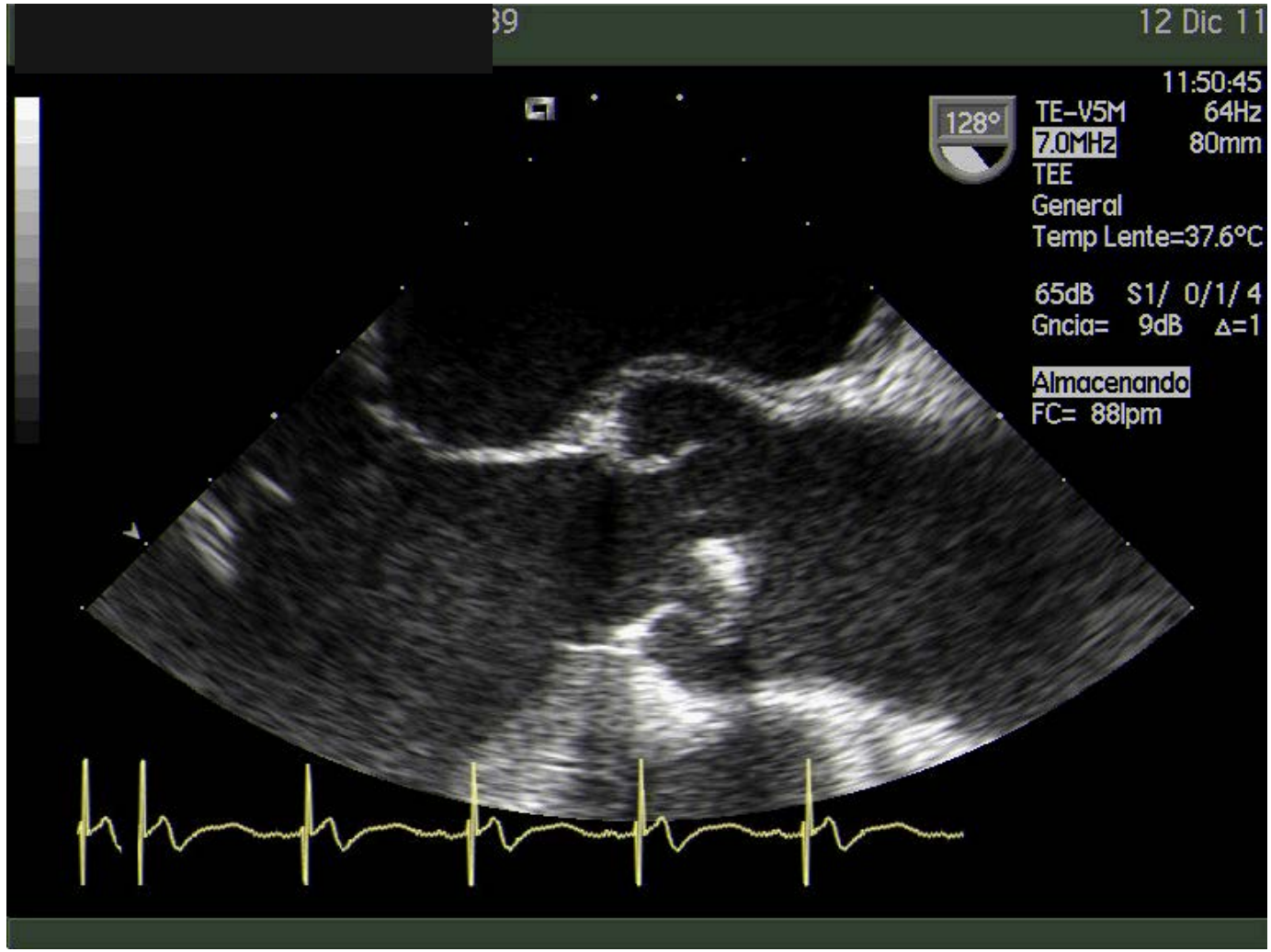
- Blood cultures (September 5th) positive for ***Streptococcus bovis***

Streptococcus bovis bacteremia

Howard S. Gold et al, www.uptodate.com

- GI tract is the most likely portal of entry
- 28% of bacteremia develop endocarditis
- *S. bovis* multivalvular endocarditis > other S. (14 *vs* 5.5)
- Highly destructive, frequent valve perforation
- Colon cancer, polyposis, colitis common underlying disease
- Antimicrobials suggested: Penicillin G, Ampicillin, Ceftriaxone, Vancomycin, Daptomycin

Echocardiography



Infective endocarditis and cryoglobulinemia ?

Manuel Ramos-Casals et al. thelancet.com. August 24, 2011

Figure 1: Classification of cryoglobulinaemia[5]

	Most frequent causes	Less frequent causes	Infrequent causes
Infections	Hepatitis C virus	HIV; Hepatitis B virus	*Streptococcus* spp; *Brucella* spp; *Coxiella* spp; *Klebsiella* spp; *Leishmania* spp; *Chlamydia* spp; *Mycobacterium tuberculosis;* leprosy; hepatitis A virus; cytomegalovirus; parvovirus B-19; chikungunya virus; Epstein-Barr virus; hantavirus; plasmodium; amoebaiasis; toxoplasmosis
Autoimmune diseases	Sjögren's syndrome	Systemic lupus erythematosus; Rheumatoid arthritis	Systemic sclerosis; antiphospholipid syndrome; inflammatory myopathies; adult-onset Still's disease; polyarteritis nodosa; giant-cell arteritis; Takayasu's arteritis; ANCA-associated vasculitis; autoimmune hepatitis
Cancer	B-cell lymphoma	Multiple myeloma	Hodgkin's lymphoma; chronic lymphocytic leukaemia; chronic myeloid leukaemia; myelodysplasia; hepatocellular carcinoma; papillary thyroid cancer; lung adenocarcinoma; renal cell carcinoma; nasopharyngeal carcinoma
Other causes	..	Alcoholic cirrhosis	Co-trimoxazole;* interferon alfa;* cocaine;* intravenous radiographic contrast;* influenza vaccination; hepatitis B vaccination; intravesical BCG; moyamoya disease; endocarditis; chilblains

ANCA=antineutrophil cytoplasmic antibodies. *Associated with cryoglobulinaemic exacerbation.

Table: Main causes associated with cryoglobulinaemia since 1990[23]

Infective endocarditis and cryoglobulinemia ?

La Civita L et al. Cryoglobulinemic vasculitis as presenting manifestation of infective endocarditis. Ann Rheum Dis 2002;61:89-90

- Two patients died due to MC and IE
- *Kingella* and *Staph. aureus*
- Association between asymptomatic MC and IE is not uncommon

Yerly P. et al. Cryoglobulins and endocarditis, a case report. Rev Med Suisse Romande 2001, 121: 573-578

Infective endocarditis and cryoglobulinemia?

Lee LC et al. "Full house" proliferative glomerulonephritis: an unreported presentation of subacute infective endocarditis. J Nephrol 2007;20:745-749

- MC ++
- Strep. Viridans
- Resolution of MC with antimicrobial therapy

Agarwal A et al. Subacute bacterial endocarditis masquerading as type III essential mixed cryoglobulinemia. J Am Soc Nephrol 1997; 8:1971-1976

- IE after treatment of MC
- *"difficulties separating infectious from non-infectious cases of MC"*
- Strep.

Take home messages

1. *Streptococcus bovis* bacteremia/endocarditis prompts examination of colon for cancer or other colonic disease.
2. Infective endocarditis (IE), although uncommon, is a cause of cryoglobulinemic vasculitis (CV).
3. Fever is present in 80 – 90% of patients with IE ….in 10 – 20% it is absent, or occasional, especially in Blood-negative Cultures IE or elderly people.
4. IE should be suspected in patients with HC virus-negative CV especially if colon disease and/or foreign bodies are present.