Clinical case presentation
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Case

A 41-year-old woman, admitted to our hospital because of one month-history of:

- Progressive exertional dyspnea,
- Paroxysmal nocturnal dyspnea,
- Orthopnea,
- Legs edema

➔ All compatible with

subacute congestive heart failure

Past Medical History

- Current smoker of 15c/day during the past 15 years
- Neither drugs, nor alcohol.
- No hypertension, diabetes, or lung / cardiovascular diseases

- **8 years before admission** she was diagnosed with

"autoimmune hepatitis and primitive biliary cirrhosis" (overlap syndrome) ➔ **ursodesoxicolic acid (700mg/d).**

One year before admission

- Legs and eyelids edema,
- Recurrent joint pain
- Skin lesions on the sun-exposed areas

→ ***systemic lupus erythematosus (SLE)***

Renal biopsy: *type V lupus glomerulonephritis*

→ **oral prednisone** (1mg/kg/d)

Clinical improvement but *persistent massive proteinuria* (>7g/d)

→ **tacrolimus** (1mg/8hours up to 2mg/8h) followed by

→ **mycophenolate** (360mg/8hours)

No proteinuria improvement.

3 months before admission,

in addition to prednisone, mycophenolate and tacrolimus, the patient started **hydroxychloroquine (200mg/d)** for persistence of skin lesions.

Day of admission

Symptoms: Dyspnea, Paroxysmal nocturnal dyspnea, Legs edema

Physical examination:

BP: 125/95mm Hg, pulse 100 bpm, Tº: 36.5ºC, SaO2: 94%.

Bilateral pedal edema, Jugular venous distention,
Bilateral pulmonary rales with prominent third heart sound at auscultation.

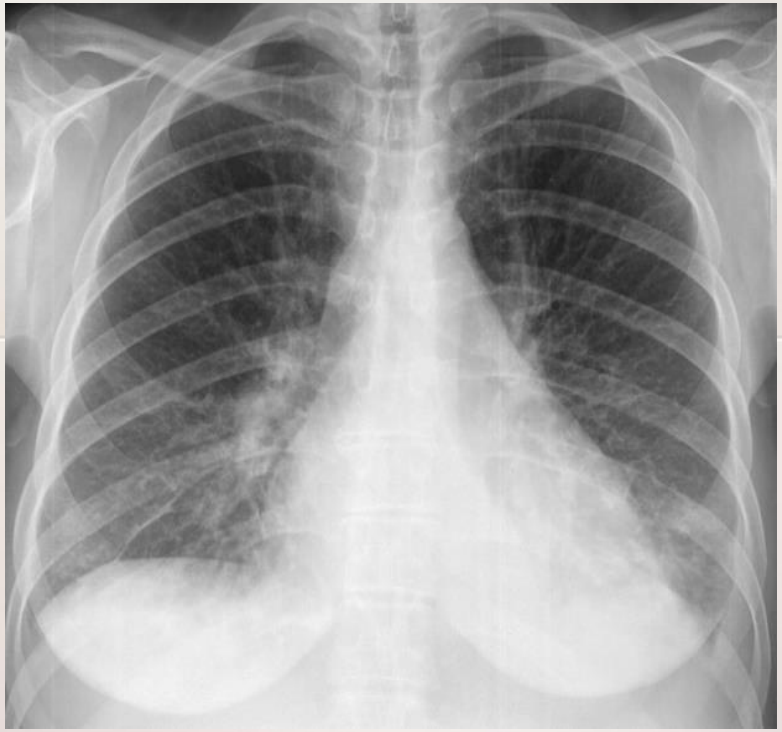
Complete blood analysis:

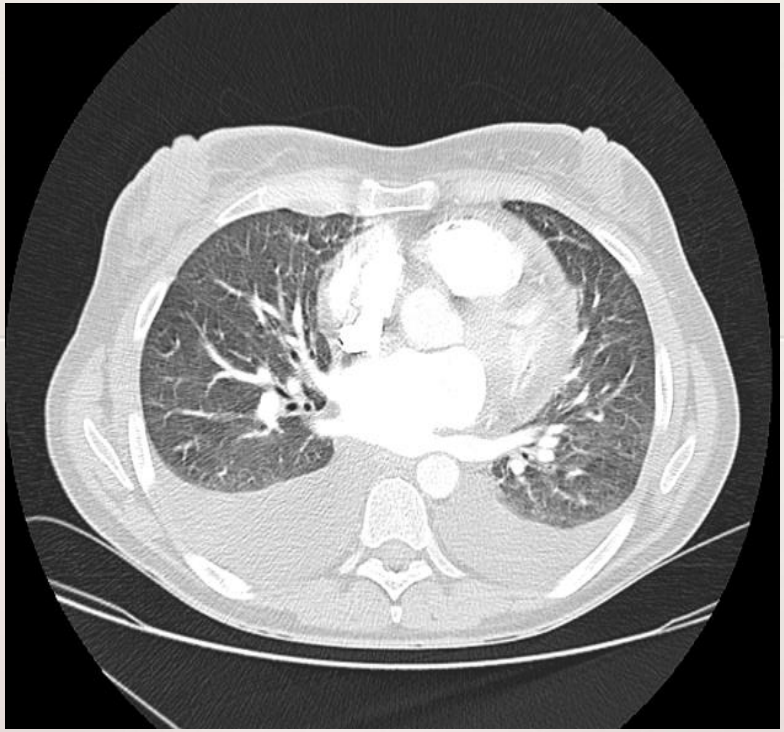
Hemoglobin, 11.8g/dL, White blood cell count, 11×109/L (72% Neutr. , 12% Lymph.) Platelet count, 360×109/L. Serum electrolytes, hepatic, and renal function were normal, ischaemic cardiac markers curve was negative.

Initial ECG and Radiology exams

ECG: sinus rhythm at 98 beats per minute, right bundle branch block without ischaemic signs.

Radiologic exams:






Suggestions
for diagnosis?
Further
investigations?

1st Main Learning Point: LUPUS & HEART DISEASE

Cardiac involvement is one of the main complications contributing to the morbidity and mortality of patients suffering from SLE.

Cardiac involvement in SLE can be summarized as follows:

→ **Pericardial disease:** the most common (usually low severity)

→ **Valvular disease:**

. mitral regurgitation (usually hemodynamically insignificant)

. valvular vegetations (Libman-Sacks endocarditis)

→ **Myocardial dysfunction**

→ **Coronary artery disease**

→ **Conduction defects** (34 to 70 % of patients with SLE)

. sequel of active or past myocarditis

. first-degree heart block is often transient

. higher degrees of heart block, and arrhythmias are unusual in adults

→ **Drug-induced cardiotoxicity: cyclophosphamide, antimalarials, phenothiazines**

Differential diagnosis of acute biventricular heart failure in our patient with SLE

-SLE Myocarditis ?

- Valvular or Ischaemic heart disease ?

- Infiltrative cardiomyopathy (amiloidosis,…) ?

- Drug-induced cardiomyopathy ?

- Endomyocardial fibrosis (sarcoidosis, scleroderma,…) ?

- Others…

Further investigations

Blood analysis: - Erythrocyte sedimentation rate and C-reactive protein normal,
- ProBNP: 8959ng/L (N < 300)
- Albumin: 26g/L (N : 35-52)

Anti-double-stranded deoxyribonucleic acid (DNA), and complement titres were within **normal limits**.

Urine analysis: Persistent massive **proteinuria** (5.5g/d).

Transthoracic echocardiography:

Left ventricular ***ejection fraction of 23%,*** associated to a ***restrictive pattern*** with ***pulmonary hypertension*** (PASP: 83mmHg), and ***high central venous pressure,*** and no cavity dilatation or valvulopathy.

Further investigations

Abdominal fat aspiration biopsy: ruled out a diagnosis of amyloidosis

Cardiac Magnetic Resonance (CMR) imaging:
Moderate left ventricular dilatation with eccentric hypertrophy
Severe left ventricular systolic dysfunction (LVEF of 28%)
Global left ventricle hypokinesia and complete lateral akinesia
The right ventricle's function was normal. Myocardial edema was not found.

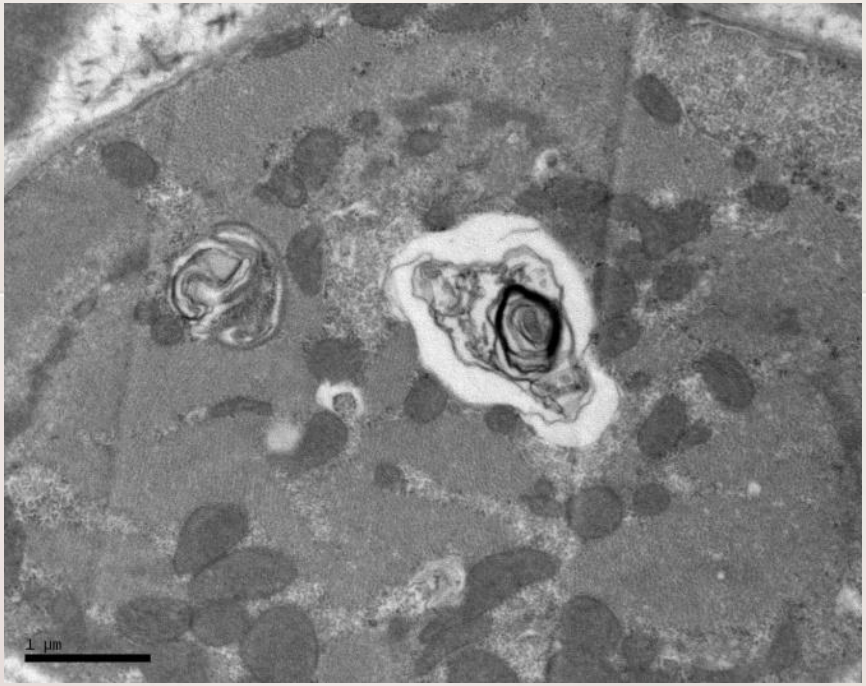
On the 15th day,
a diagnostic test was performed.
… suggestions ?

Cardiac catheterization with Endomyocardial biopsy

Cardiac catheterization demonstrated normal coronary arteries

Endomyocardial biopsy
(Optic and electron microscopy)

. Preserved myocardial architecture
. Vacuolar myopathy
. Myelin figures (myeloid bodies)



Final diagnosis

Infiltrative cardiomyopathy due to hydroxychloroquine

Optic and electron microscopic constellation of findings
highly suggestive of **toxic myocardiopathy due to hydroxychloroquine**

1. Preserved myocardial architecture - Ok
2. Absence of sign of myocarditis - Ok
3. Vacuolar myopathy - Ok
4. Myeloid bodies – Ok
5. Curvilinear bodies, which are considered the most specific when present.

In our patient we were not able to demonstrate the presence of curvilinear bodies

Treatment and evolution

4 weeks after admission, the patient was discharged with

→ prednisone, 20mg per day
→ mycophenolate, 360mg/12hours,
→ tacrolimus, 2mg/12hours,
→ diuretics, hydralazine, ACE inhibitors, and ß-blockers

3-6-12 months of outpatient care follow-up

New **transthoracic echocardiography** and **CMR**:

→ persistence of LV dilatation and LV systolic dysfunction (LVEF of 30%)
→ late gadolinium enhancement studies of CMR excluded myocarditis
. non-ischaemic disease
. absence of myocardial edema.

2nd Main Learning Point: HYDROXYCLOROQUINE & CARDIOTOXICITY

Host factors contributing to antimalarial cardiotoxicity remain unclear

Large cumulative dose raises the likelihood for toxic myocarditis

Two different forms of cardiac toxicity have been described:

→ **Conduction abnormalities:** right/left bundle-branch or atrioventricular block

→ **Infiltrative cardiomyopathy:** much less frequent

. Restrictive pattern with biventricular hypertrophy → Dilated myopathty
. Definitive diagnosis by endomyocardical biopsy with the findings described.

What is particular in our case?

→ **Rapid onset of cardiomyotoxicity :** only after a 3-months period of treatment
→ **Relative low cumulative dose of hydroxychloroquine :** 16 grams

Literature review

→ **Only one previous described case** with a similar low cumulative dosage (15 grams)
(*patient with recurrent malaria treated repeatedly with chloroquine*)

Our Hypothesis

Drug interaction with Tacrolimus raising hydroxychloroquine serum levels and, subsequently, toxicity

Persistent low serum albumin due to nephrotic syndrome reduced hydroxychloroquine renal excretion and, subsequently, raised serum levels and toxicity

Final Key Points

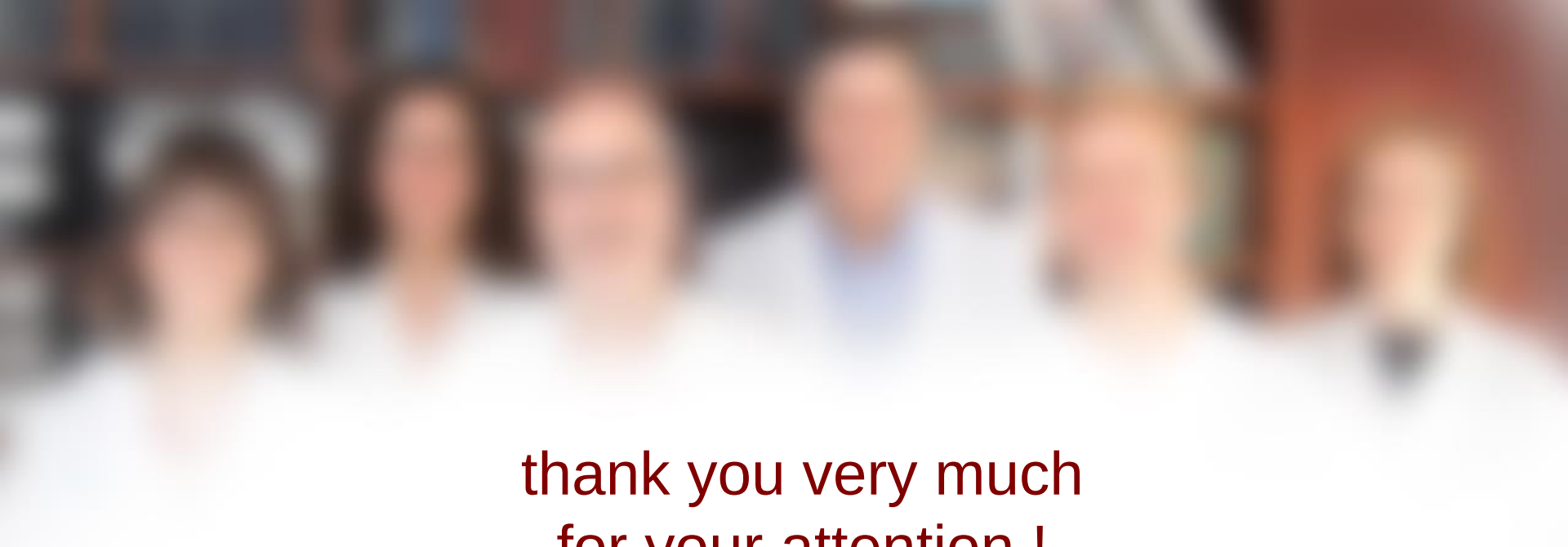
New onset of
heart failure or conduction abnormalities
in SLE patients with high cumulative dose of
chloroquine/hydroxychloroquine

Drug-related myocardial toxicity
should be suspected

Exceptional !!
In patients with “low cumulative dose”...
rule out predisposing factors for
raising CQ/HCQ serum levels !!

Prognosis of cases reported:

Despite hydroxychloroquine withdrawal, **prognosis remains uncertain**, varying from complete recovery to need of cardiac transplantation or death.



thank you very much
for your attention !

Bellvitge
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Professionals de Referència