The Mediterranean experience: lessons learned and current challenges

Visceral leishmaniasis-HIV coinfection: current challenges and perspectives

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Lessons learned

to learn, no previous experience on co-infected patients
to build up knowledge, to describe and to communicate our experience and findings
to work together, for patient series, for clinical trials and for a surveillance network

Leishmania and Human Immunodeficiency Virus Coinfection: the First 10 Years

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The Relationship between Leishmaniasis and AIDS: the Second 10 Years

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• 1985: first case of HIV/VL co-infection recorded (in Spain)

• Before 1985 (Spain): 70% of VL in children <15 yo; 1997: 75% in adults 29-33 yo (60% HIV+)

• 1990’s (Spain): 15% (7-17%) of febrile HIV: amastigotes in bone marrow

• 1990’s (Spain): collaborative Spanish group for VL/HIV study

• 1994: WHO dedicated surveillance network (13 reporting sites increased to 16 sites in 1998)
Leishmania & HIV synergy
Th$_2$ persistent response

- HIV increased the risk of VL
  - By 100-2300 times in endemic areas
  - Reactivation of a latent infection
  - Primary infection
  - Relapse
  - Reinfection

- VL induces AIDS progression
  - > HIV load
  - < CD4 count
  - Poor increase in CD4+ in relapsing patients compared with that in non-relapsing patients despite undetectable HIV viral load

WHAT WE HAD AT THAT TIME: passion, bone marrows & antimonials
WHAT CAME YEARS LATTER: knowledge, PCR, liposomal AB & HAART
1995 (WHO): 858 cases, 729 from Europe, 450 from Spain (53% of all reported HIV/VL co-infections recorded in the world)

2-9% AIDS patients in Southern Europe will develop VL

1990-2006: 2210 cases in southern Europe (57% in Spain)
- Incidence peak during 1996-1998
- 1996-1997: HAART
- Steadily decrease during 1998-2001
- Low incidence plateau after 2006
DEMOGRAPHICS

- Mean age: 38-39 yo **adults**
- Gender: 83-85% **male**
- **IVDU ++ affected:** from 76% (1990-8) to 67% (2001-6)
  - live in peri-urban environment
  - transmission sharing syringes **(artificial-epidemic-anthroponotic cycle)**
  - secondary reservoirs: +++ parasites in the peripheral blood **(50% in monocytes; 67% in buffy-coat culture, 100% by xenodiagnosis)**
THE PARASITE

- 3 main cryobanks/identification centers were designed
- *Leishmania infantum*

Enzymatic characterization of VL cases
- extreme variability (28 different zymodemes): MON-1 (66%), MON-24 (13%)
- new zymodemes never described
- low-virulence dermotropic variants
- recombinative variants
- no correlation with clinical expression
- *L. infantum-L. major* hybrid strains
- *Leishmania*-like flagellates (nonhuman trypanosomatids)

- PCR + RFLP analysis for *Leishmania* characterization
VL DIAGNOSIS

• **Serology**
  – 40% one test serology is negative
  – 15-20% all test serology (CIE, IFAT, ELISA, WB) are negative
  – serology +ve in reactivations and –ve in primary infections?

• **Bone marrow aspirate and biopsy staining & culture**
  – 74-98% in first episode
  – 64% in relapses
  – Culture increases sensitivity

• **Lymph node & spleen & liver biopsy or aspirate staining & culture**
  – Spleen: 95-96%
  – Liver: 77-91%
  – Lymph node: 52-59%

• **Peripheral blood staining & culture**
  – Staining: 50-53%
  – Buffy-coat culture: 67%

• **Can be found in any place**
  – mouth, larynx, gastrointestinal tract, rectum, pleura, lungs, mediastinum, pericardium, suprarenal glands, CSF…
CLINICAL MANIFESTATIONS

• **CD4 count**
  - <200/mm³ in 80-99%
  - 200-500/mm³ in 7-22%
  - >500/mm³ in 0-3%

• 42-72% **AIDS defining criteria** before/during 1ˢᵗ episode of VL

• 42-68% **concomitant opportunistic infection** during any episode of VL
  - disseminated tuberculosis
  - atypical mycobacteriosis
  - lymphoma
  - salmonellosis
  - disseminated CMV
  - toxoplasmosis
  - pneumocystosis
  - cryptococcosis…
• **Broad spectrum:** from asymptomatic disseminated and fatal cases

• **Cutaneous CL (4%)**
  – Healthy skin
  – Exclusive cutaneous
  – Mucocutaneous: nasal, oral, pharynx and larynx
  – Diffuse cutaneous: non-ulcerated papulonodular, dermatomyositis-like…
  – Concomitant with Kaposi’s sarcoma, herpes, varicella-zoster, tattoos…

• **CL + VL**
  – CL (ulcer) can precede (even months) VL
  – CL concomitant with VL
  – CL after VL treatment (diffuse cutaneous)

• **Typical VL: bone marrow, spleen, lymph nodes (94%)**
  – Not significantly different from those HIV-
  – Fever (80-95%), constitutional syndrome, splenomegaly (54-90%), hepatomegaly (34-85%), pancytopenia (35-77%), thrombocytopenia (52-93%), adenopathies (12-57%)

• **“Atypical” VL**
  – Digestive tract: chronic diarrhea
  – Respiratory tract: pleural effusion, pneumonitis, mediastinal adenopathies
  – Multiorgan dissemination
TREATMENT

• Sb5+: 20 mg/Kg/d/iv/28 d
  – Resistance after repeated treatment
  – Toxicity: pancreatitis and heart toxicity (Q-Tc, AV-block)

• AB: 0.7 (0.5-1) mg/kg/d/iv/28 d (15-25 mg/kg total dose)
  – Toxicity: fever, chills, veins inflammation, thrombophlebitis, kidney failure and anemia

• LAB: 4mg/kg/d daily or intermittently for 10 doses (40 mg/kg total dose)
  – Similar to AmB deoxicolate in its efficacy
  – Less toxic than AmB deoxycholate
  – Recurrences could be treated with LAB as not described resistance

• Pentamidine: 4 mg/Kg/d /iv/14-21 d

• Allopurinol; Ketoconazole; Fluconazole; Itraconazole, Miltefosine orally combined or combined with parenteral treatment. No good data on the efficacy of combination therapy

• Interferon gamma (IFNγ) 100 μg/m2/d x 28 days

• Selective splenectomy

• Systematic parenteral treatment for CL to prevent dissemination
**CLINICAL COURSE**

- **Co-infection is characterized by**
  - Lower cure rates
  - Higher drug toxicity
  - Higher relapse rates (up to 9% can be re-infections)
  - Higher mortality rates

- **Initial cure** rate 56-90%

- **Adverse effects**
  - Sb\(^{5+}\): 56% (SAE: 28%, fatal AE: 12%), mainly pancreatitis and arrhythmias
  - AB: renal toxicity (18-36%), anemia

- **Relapsing course** after a correctly treated 1\(^{st}\) VL episode
  - 60% relapse at 6-9 months
  - 90% relapse at 12 months
  - Relapsing time is shorter with future relapses
  - Clinical features of relapses are comparable with initial episodes
• Primary prophylaxis was not indicated

• Antimonials: 20 mg/Kg/d/21-28d
• LAB or ABLC: 3-5 mg/Kg/21-28d
• Pentamidine: 4 mg/Kg/21-28d

• Miltefosine (100-150 mg/d)
• Itraconazole + Allopurinol
• Itraconazole + Miltefosine

• Once the patient had recovered his immune function with HAART (CD4+ >200/µl for >6 months) and the VL was quiescent, suspension of the prophylaxis can be considered.
TEST OF CURE/FOLLOW UP

• A parasitological cure is not indicative of an absence of future relapse
• A clinical cure does not necessarily indicate parasitological clearance

• **Bone marrow** aspirate/biopsy performed at 1 month and 6 month. Patients refuse successive bone marrow aspirate/biopsy: is an invasive and painful technique

• **Urine latex** agglutination antigen detection test (no relapse if repeatedly negative)

• **Nested-PCR in peripheral blood** (+ does not mean relapse, but excellent negative predictive value). RTQ-PCR sensitivity of 0.001 parasites/ml
PREDICTORS OF VL RELAPSE

- CD4+ count <100 cells/µL at the time of 1st VL episode
- Previous history of VL relapse
- Lack of secondary prophylaxis
- Absence of an increase in CD4+ treated with ARV

Relapsing patients show a lower CD4 count increase

(Cota GF. PLoS Negl Trop Dis 2011)
SURVIVAL

- Mortality rate during 1st episode was 10-19% and can reach up to 24% during the month following termination treatment, mainly because drug-toxicity and opportunistic infections.

- Mean survival time is 4-12 months, and the mortality rate at 12 months of 1st episode is 60%.

- **Predictive survival factors**
  - HAART
  - High CD4+
  - Maintenance therapy
HAART

- 1996-7: introduction in Europe
- Reduces morbidity and mortality
- Greatly reduces the incidence of symptomatic first episode of VL
- Reduces the risk of relapse. VL relapse even with undetectable viral load (81% had undetectable viral load at the time of VL relapse)
- The period between relapses is prolonged
- Some cases of immune-reconstitution-disease (IRD): VL, diffuse cutaneous, PKDL…

- Leishmaniasis is an AIDS-defining disease (WHO) and a reason to start HAART independent of the CD4 count
- Protease inhibitors have in vitro activity against *Leishmania*
Current challengers

Immigration and travel

Non-HIV immune suppressed patients

Transplant

anti-TNF drugs

Climate change
Mediterranean Chef’s recommendations for VL/HIV co-infection

• To suspect VL in any febrile HIV patient
• To diagnose *Leishmania* infection promptly: bone marrow/ spleen/ liver/ blood samples by staining/ culture/ PCR
• To treat with liposomal AB (40 mg/Kg), combination of drugs?
• To start ARV treatment
• Test of cure?
• To initiate secondary prophylaxis just after treatment
• To follow up patients closely & quantitative PCR in blood
• To be aware of atypical relapses