NNRTIs (23 to nevirapine, 11 to efavirenz, and 5 to both). None had prior or ongoing exposure to RPV or etravirine (ETR). Evidence of RPV resistance (%, IC95%) was found in 16/112 (14.3%, ±6.4) patients: 5/52 (9.6%, ±8) in naive and 11/60 (18.3%, ±9.7) in experienced HPW. Ten individual RPV RAMs were identified, with an overall prevalence of 4.5% (±3) for E138A; 3.6% (±3.4) for E138K; 2.7% (±3) for Y181C; 1.8% (±2.4) for Y188L and H22Y; 0.9% (±1.7) for E138G, E138Q, K101P, V179L and Y181I. The combination L100I+K103N was found in 2/60 (3.3%, ±4.5) experienced HPW, in one case associated with E138K mutation. Prior NNRTI (either efavirenz or nevirapine) use was observed in 91% experienced patients harboring RPV RAMs, with a median (IQR) exposure of 24 (6–115) months. No association with any subtype was found. Individual RPV RAMs profile, ART exposure and predicted RPV susceptibility are shown in Table 1. All naive pregnant women with RPV RAMs had evidence of, at least, reduced susceptibility to RPV while 9/11 (82%) experienced HPW had predicted intermediate or high level resistance. Despite the limited period of time and number of patients, some aspects should be highlighted. In a population of experienced HPW, 18.3% of patients had RPV resistance considering either individual RPV RAMs, L100I+K103N combination or both, which can be mostly attributed to prior exposure to first generation NNRTIs. In this context, a reduction in the susceptibility to the drug was observed in the majority of experienced patients harboring RPV RAMs. Anta et al. recently described that 19.3% genotypes from patients failing NNRTIs are RPV-resistant. Considering exclusively NNRTI-experienced HPW in our cohort, 25% should be considered RPV-resistant (data not shown). Of note, none of our patients had exposure to ETR, which shares RPV’s resistance profile. However, the highest burden of RPV resistance was in women infected perinatally (8 of 11 patients) and had been heavily exposed to NNRTI-based ART, with irregular adherence. In this clinical scenario, cross RPV resistance could emerge as a result of long term non-adherence to first generation NNRTIs. Considering the naive patients, these preliminary data show a moderate prevalence of RPV RAMs. Reports of RPV RAMs in naive patients are limited.9 Chueca et al. described an overall 7.7% RPV RAMS in HIV-1 infected patients, being E138A present in 5.5%.10 Such prevalences are lower than those described here. The prevalence of RPV RAMs in naive HPW could be attributed, to cross resistance to first generation NNRTI-selected and, subsequently, transmitted drug-related mutations. As E138A polymorphism is one of the most prevalent RPV RAMs, development of a validated score could be clinically useful. Further research is needed to evaluate if HIV subtype has an influence in RPV resistance. Our study supports routine genotyping before prescribing RPV in this population.

Conflict of interest

All authors declare no competing interests.

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References


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right nasal vestibular induration of three weeks progression. He also noted a nasal purulent discharge, which caused special discomfort at night for the previous five weeks. He had a history of CL on his left leg during 2011, confirmed by PCR L. infantum var lombardi infection and treated with weekly intralesional meglumine antimoniate with healing of the lesion. On examination, the right vestibule and nasal septum were erythematous and indurated. On the anterior nasal septum mucosa, a nodular lesion without ulceration was observed. Blood test results showed a slight elevation of C-reactive protein, normal CD4+ and CD8+ T lymphocytes count and HIV test was negative. A nasal cytology and a skin biopsy were performed, showing Leishmania amastigote forms (Fig. 1), and were then processed by nested-PCR with a posterior phylogenetic analysis based on the nucleotide sequences to discriminate the Leishmania strain. L. infantum var lombardi infection was confirmed. The CT scan showed thickening of the right nasal vestibule and the nasal mucosa without cartilage affectation. Abdominal ultrasound and IgG anti-Leishmania were negative. Treatment with intravenous liposomal amphotericin B was started, with a total dose of 18 mg/kg. Three months after the initial therapy, the erythema and induration clearly improved, a control biopsy-PCR for Leishmania was negative and the patient’s symptoms resolved. After 14 months of follow-up, the patient was asymptomatic.

An urban community outbreak of CL and visceral leishmaniasis in the south-west of Madrid had started in July 2009 as reported by Arce et al., with a total of 446 cases up to December 2012; 160 (35.9%) had visceral and 286 (64.1%) exclusively cutaneous forms of the disease, and the cases were confirmed with L. infantum infection. The patient had not traveled before to other countries or areas that were highly endemic for Leishmania; therefore, the infection cannot be considered imported. The antecedent of CL in the patient in association with the clinical progression of nasal lesions enhances the diagnosis of MCL, differentiating this to the exclusive mucosal leishmaniasis observed in Europe. In the literature reviewed, two immunosuppressed Italian patients with MCL were found; one under multiple immunosuppressive therapy, confirmed with L. infantum infection and the other an HIV positive patient with no molecular confirmation. The course of the described patient was favorable, and he did not show signs of systemic disease with completed resolution of the infection after treatment with liposomal amphotericin B, an antifungal drug with excellent results in treatment of MCL in Europe. This is the first case that demonstrates that L. infantum var lombardi, which is a genotype routinely isolated from Madrid, can cause MCL even in immunocompetent patients. It is important to highlight that MCL could be a clinical presentation form of leishmaniasis in travelers returning from Spain, where L. infantum is endemic and should be considered as an infection to initiate a prompt treatment to avoid devastating complications.

Conflict of interest

The authors declare no conflicts of interest and contributed equally to this article.

References


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