

Reactivation of Tuberculosis during Dual Therapy with Pegylated Interferon and Ribavirin for Chronic Hepatitis C about a Case

D. Soro*, S. Koné, A. Ouattara, A. W. Ndjitoyap, A. J. B. Okon, D. Diallo, C. Assi, K. E. Allah, M. J. Lohoues Kouacou, B. M. Camara

Service d'Hépatogastroentérologie, CHU Cocody, Abidjan, Côte d'Ivoire
Email: [*drambake@yahoo.fr](mailto:drambake@yahoo.fr)

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Abstract

The infection by the virus of the hepatitis C can be associated with other infectious diseases, including the viral and bacterial infections of which the tuberculosis. The infection to *Mycobacterium tuberculosis* can remain latent during several years and show itself during a state of immunosuppression. The role of the antiviral treatment in the reactivation of the tuberculosis is debated. We bring back an observation of tubercular reactivation during dual therapy with pegylated interferon and ribavirin for a viral chronic hepatitis C. A virologique answer slow was obtained in the 40th week, as well as the reactivation of the tuberculosis. The tuberculosis was of ganglionic localization at our patient. The antituberculous treatment was established while maintaining the treatment. The evolution of the tuberculosis under treatment was favorable but for the VHC, we noted a virologique answer with premature relapse.

Keywords

Chronic Hepatitis C Virus, Tuberculosis, Treatment

1. Introduction

Chronic infection with hepatitis C virus (HCV) can be associated with other infectious diseases whether viral infections (HIV and HBV), bacterial infections such as tuberculosis or sexually transmitted diseases [1]. The

*Corresponding author.

association of chronic hepatitis C to tuberculosis has been described with a prevalence of 3.3%. Tuberculosis infects about a third of the world population [2] can remain dormant for several years and be in a state of immunosuppression. Reactivation of tuberculosis induced antiviral therapy for chronic hepatitis C was reported in the literature but the link remains controversial. We report a case of tuberculosis reactivation occurred during antiviral therapy (pegylated interferon and ribavirin) for chronic hepatitis C.

2. Case Report

Miss NAB Ivorian 56 years old, with a history as a blood transfusion 10 years ago following a hysterectomy, carries a viral hepatitis C chronic active, diagnosed in 2010, genotype 1b with a high viral load of 7,441,824 IU/ml, strong cytolytic to 6.8 times the upper limit of normal (ULN) for ALAT, $3.6 \times$ ULN for ASAT and an estimated A3F4 by Actitest Fibrotest and histological activity. The patient was asymptomatic with a body mass index (BMI) 22 kg/m^2 . The indication for treatment with combination therapy with pegylated interferon alpha 2a plus ribavirin was made. The clinical assessment including blood count, urea, glucose, creatinine, prothrombin time, the protidogramme, lipid and hormonal assessment were normal. The HIV serology and HBV were negative. The gamma-glutamyl transferase to 4 times normal and normal alpha-fetal protein. Upper gastrointestinal endoscopy, abdominal ultrasound and chest X-ray were normal. Treatment was established in November 2010 with pegylated interferon-2a (PEGASYS^R) at a dose of $180 \mu\text{g/week}$ subcutaneously plus ribavirin (COPEGUS^R) at a dose of 1000 mg/day in two divided doses orally.

The response to treatment was marked by the persistence of biochemical activities (transaminases 2.5 times normal) associated with leukopenia ($3300/\text{mm}^3$), neutropenia ($1216/\text{mm}^3$), normochromic normocytic anemia (9.3 g/dl) and thrombocytopenia ($106,000/\text{mm}^3$). The patient received red blood cell growth factors based Reccormon^R $30,000$ subcutaneously and slow viral response was achieved in 40 weeks.

At week 40, the patient presented with an extra firm and mobile right clavicular lymphadenopathy with signs of tuberculous impregnation. There was a marked absence of pulmonary signs and urinary ascites. Abdominal ultrasound (**Figure 1**) found deep abdominal lymph nodes, liver homogeneous regular contours and confirmed the absence of ascites.

The tuberculin skin test was phlyctenular. A chest radiograph was normal. The search for *Mycobacterium tuberculosis* was negative in the liquid sputum and urine. A lymph node biopsy was performed which pathological examination showed epithelioid granulomas with giant cell caseating confirming the diagnosis of lymph node tuberculosis (**Figure 2**). Antituberculosis quadruple therapy pyrazinamide (1800 mg/day), isoniazid (300 mg/day), rifampicin (600 mg/day) and ethambutol (1500 mg/day) was established for a period of two months followed by two drugs (isoniazid 300 mg + rifampicin 600 mg) for four months. The total duration of tuberculous treatment was six months. With treatment, the outcome was marked by the disappearance of lymphadenopathy and signs of tuberculous impregnation. Antiviral treatment was continued until the 96th week still undetectable viremia. Stock control six months after cessation of antiviral therapy was marked by early relapse with viremia to 273 IU/ml (2.44 log).



Figure 1. Ultrasound image of a deep abdominal lymphadenopathy.

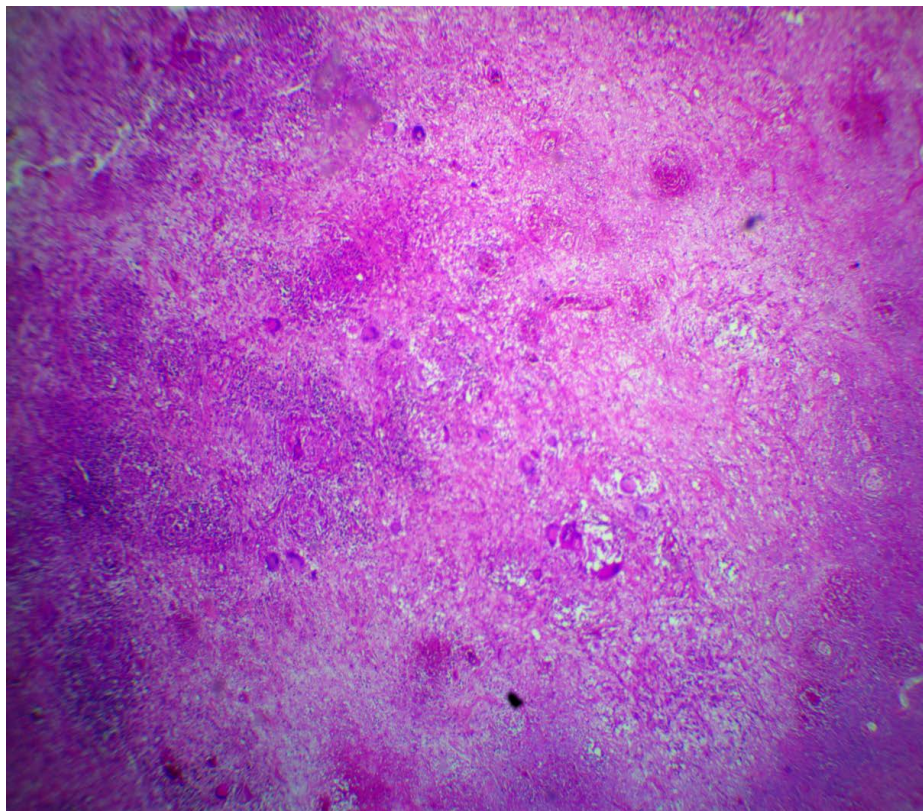


Figure 2. HE \times 100 granulomatous reaction made of epithelioid cells, Langhans-type giant cells and a lymphocytic crown centered caseous necrosis.

3. Discussion

Infection with the hepatitis C virus (HCV) may predispose them to other infectious diseases, viral or bacterial. Thus, a multicenter case-control study showed a higher incidence of infections in patients infected with HCV compared to controls (3.3% versus 1.3% for tuberculosis) [1]. Impairment secondary to infection with this virus immune mechanism has been suggested. Indeed, HCV appears to be able to replicate within mononuclear peripheral blood cells, thus compromising their antimicrobial activity [3]. In the Ozyilkan *et al* study, it was noted a reduction in the number of CD4 + T lymphocytes and CD4/CD8 ratio in patients with HCV positive serology [4]. The reasons for the occurrence of tuberculosis in immunocompetent patients and HCV remain unclear. It has recently been demonstrated that HCV-stimulated endogenous interferon α . This active in CD4 T cells, the gene for interferon-gamma involved in the control of mycobacterial infections [5]-[7]. Reactivation of tuberculosis during antiviral therapy for chronic hepatitis C is exceptional. Only four cases have been previously reported in the literature known. The first observation was published in 2006 by Sabbatani *et al.* [8]. He was a 62 year old patient treated for chronic hepatitis C with pegylated interferon and ribavirin and who experienced severe pulmonary tuberculosis in the seventh month of treatment. Antiviral treatment was maintained and the tuberculosis treatment has a favorable development [8]. The second case was reported by Farah *et al.* in 2007 [9] this was a patient treated for chronic hepatitis C combination therapy with standard interferon and ribavirin, complicated by pulmonary tuberculosis [9]. The last two cases were reported by Belkahla [10] this was urinary tuberculosis in a patient with lymph node and another.

We report a case of tuberculosis reactivation antiviral therapy (pegylated interferon and ribavirin) for chronic hepatitis C; it was lymph node tuberculosis. Virologic response was slow in our patient, who required 96 weeks of combination therapy, triple therapy is not available at this time in our resource-limited unlike the two cases reported by Belkahla or rapid virologic response [10]. The evolution of tuberculosis was favorable anti tuberculosis quadruple [11] as in other observations reported [8]-[10]. In our case, there was an early relapse 6 months after discontinuation of combination therapy.

Several hypotheses to explain the reactivation of tuberculosis by antiviral therapy have been advanced. Eradication of the virus by treatment could affect mycobacterial infection through a cessation of stimulation of endogenous interferon- α . The coincidence of tuberculosis reactivation with the negativity of viremia in our patient supports this hypothesis. Furthermore, interferon could occur through iatrogenic immunosuppression by inducing buffy neutropenia [12], as in our case. Finally, antiviral treatment may be decreasing the number and altering the function of CD4 + T cells [13].

Conversely, a possible protective role of interferon- α against *Mycobacterium tuberculosis* was reported. This was a patient with pulmonary tuberculosis aggravated by stopping interferon- α , prescribed for chronic hepatitis C [14].

4. Conclusion

Reactivation of tuberculosis by the antiviral treatment of chronic hepatitis C is possible, although exceptional. It appears from the reported cases in the literature and our observation that tuberculosis can be pulmonary or extra pulmonary seat. Antiviral treatment can be maintained in combination with TB treatment. Screening for TB in highly endemic countries, in subjects with a history of tuberculosis or a concept of contagion could prevent reactivation in patient candidates for antiviral therapy.

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