

# Lymph node enlargement during combination therapy for chronic Hepatitis C with pegylated Interferon alpha and Ribavirin: harmless reaction or harmful disease?

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## Summary

**Background:** Perihepatic lymph node enlargement (LNE) is often present in patients with chronic hepatitis C (CHC) and correlates with the degree of inflammation, as well as the stage of fibrosis of the liver [1, 2]. LNE at sites distant from the liver hilum, however, is not a common feature of chronic hepatitis but may occur during antiviral therapy as we report here.

**Objectives:** The aim of this study was to examine the frequency and aetiology of LNE at sites distant from the liver hilum in patients with chronic hepatitis C during combination therapy with pegylated interferon alpha and ribavirin.

**Methods:** The charts of all patients undergoing therapy with PEG and RIBA for CHC at our institution from January 2002 to April 2003 were re-

viewed for those who developed de novo LNE at sites distant from the liver hilum.

**Results:** In total, 8/217 patients (3.7%) or 5/125 patients treated within clinical trials (4.0%) were recorded to have developed *de novo* LNE during antiviral therapy.

**Conclusion:** LNE at various sites distant from the liver hilum was observed in up to 4% of our patients during treatment of CHC with PEG and RIBA. While being reactive in nature and resolving upon cessation of therapy in the majority of patients *de novo* LNE may be due to serious disease and warrants further investigations.

**Key words:** lymph node enlargement; pegylated interferon; ribavirin; chronic hepatitis C

## Introduction

Combination therapy with pegylated interferon alpha (PEG) and ribavirin (RIBA) is currently the standard treatment for patients with CHC. However, side effects are numerous and include commonly fatigue, a flue-like syndrome, gastrointestinal disturbances, neuropsychiatric alterations and haematologic abnormalities. Infrequently also serious adverse events are reported, including severe depression up to suicidal attempts, hearing loss, interstitial pneumonitis, and triggering of autoimmune diseases. In a large clin-

ical trial, the overall frequency of side effects has been found to be higher than 20% [3]. While the mechanisms of antiviral action for this interferon-alpha based therapy remain ill-defined, they are likely to include direct antiviral and immunomodulatory effects. As a consequence of the

immunomodulatory effects of interferon, reactivation of sarcoidosis with lymph node enlargement (LNE) has been described [4].

The aim of our study was to determine the frequency and aetiology of LNE during antiviral therapy for CHC.

### Abbreviations

LNE	Lymph node enlargement
CHC	Chronic hepatitis C
PEG	Pegylated interferon alpha
RIBA	Ribavirin
NHL	Non Hodgkin lymphoma
TBC	Tuberculosis
IVDU	Intravenous drug users

## Patients and methods

The charts of all patients undergoing therapy with PEG and RIBA for CHC at our institution from January 2002 to April 2003 were reviewed for those who developed *de novo* LNE at sites distant from the liver hilum.

## Results

During the observation period, 217 patients with CHC were treated with PEG and RIBA, 58% within controlled trials. In total, 8/217 patients (3.7%) or 5/125 patients treated within clinical trials (4.0%) were recorded to have developed *de novo* LNE during therapy. 4/8 patients were investigated further by aspiration cytology or surgical resection. In 2/8 (25%) patients, LNE was due to non-Hodgkin lymphoma (NHL) and tuberculosis (TBC), respectively. LNE of the remaining 6 patients (75%) was reactive in nature,

which was proven either by cytology/histology and/or by its clinical course with rapid resolution upon cessation of treatment.

Details of the individual patients are shown in table 1. Most were infected with genotype I. There was no patient infected with HIV. Patients 1–6 were former IVDU. The appearance of LNE did not depend on the dose of PEG and RIBA or the duration of treatment. There was no difference in treatment response of patients with LNE compared to patients without LNE.

**Table 1.**  
Characteristics of 8 patients with LNE during antiviral therapy with PEG and RIBA.

Age/Sex (yrs, M/F)	Geno-type	PEG (Dose/wk)	RIBA (Dose/day)	Site of LNE	Time of onset (treatment week)	Treatment response	Histology/Cytology
43 F	3a	1.5 µg/kg	800 mg/d	Inguina/Axilla	16	Sustained responder	Reactive
37 F	1b	1.5 µg/kg	800 mg/d	Axilla	12	Relapser	None
16 F	1a	180 µg	None	Inguina	21	Relapser	None
42 F	1a	180 µg	800 mg/d	Neck	42	Sustained responder	None
46 F	1b	180 µg	1000 mg	Inguina	19	Sustained responder	Reactive
55 M	1b	45 µg	1200 mg	Neck	29	Relapser	NHL
50 M	1b	1.5 µg/kg	1200 mg	Inguina	40	Sustained responder	None
57 M	1b	180 µg	1000 mg	Neck	36	Sustained responder	TBC

## Discussion

In all cases, reactive LNE resolved spontaneously and as a result, may have been an expression of the immunomodulatory effects of PEG and RIBA due to the promotion of virus-specific proliferative T-cell responses as observed by Barnes et al. [5].

Whether the manifestation of NHL in one patient was related to antiviral therapy or a coincidence remains unclear. Because of a higher prevalence of hepatitis C in patients with NHL [6], we speculate that the appearance of this disease is a coincidence rather than an effect of RIBA or PEG.

The reactivation of TBC occurred in a female health care worker with CHC, who was exposed to TBC 30 years before. After developing cough and dyspnea during the antiviral treatment, swelling of a supraclavicular lymph node was recognised at treatment week 36. Histology of this lymph node showed necrotising granulomatous lymphadenitis. Culture of this tissue was positive for *M. tuberculosis*. Three samples of morning sputum also revealed mycobacteria. A high resolution CT-scan of the chest showed mediastinal and hilar lym-

phadenopathy but no typical signs of active TBC. The LNE resolved within months under tuberculostatic therapy. Six months after antiviral combination therapy, HCV-PCR was negative and the patient was defined as a sustained responder.

A reactivation of TBC during treatment with RIBA and PEG has not yet been reported. Only one case report has been published, where interferon treatment led to the aggravation of a tuberculous pleurisy [7]. Although the mechanism is unknown, it has been shown in vitro, that interferon treatment impairs the activity of human monocytes and macrophages, which are no longer able to control the growth of *Mycobacterium bovis*. These results provide some evidence that the IFN-alpha might facilitate mycobacterial growth in patients harbouring these organisms [8].

No cases of sarcoidosis developed under treatment with PEG and RIBA in our study. Since this phenomenon has been reported [4], sarcoidosis should also be taken into consideration if LNE occurs during antiviral therapy.

In conclusion, we report that LNE at various

sites distant from the liver hilum was observed in up to 4% of our patients during treatment of CHC with PEG and RIBA. While being reactive in nature and resolving upon cessation of therapy in the majority of patients, *de novo* LNE may be due to serious disease and warrants further investigations.

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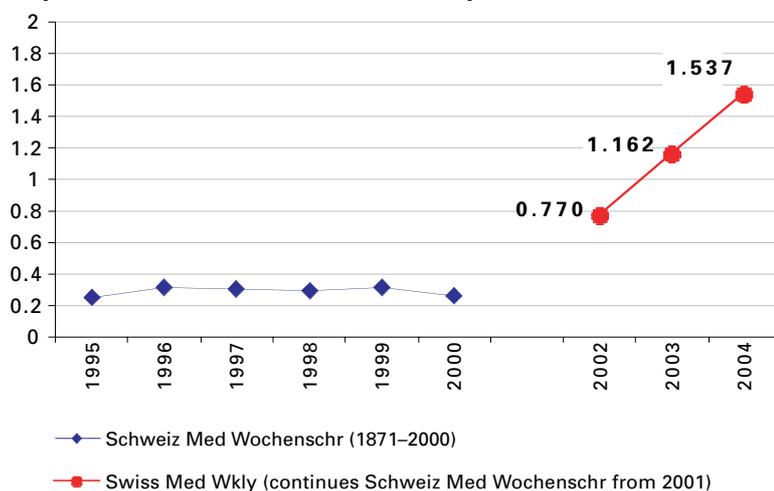
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