ANNALS OF HEPATOLOGY

Volume 3 *Number* 3 *July-September* 2004

Article:

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Annals of Hepatology 2004; 3(3): July-September: 118-120

Case report

Enlarged cervical lymph nodes and elevated liver chemistry tests: a therapeutic dilemma

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Abstract

We describe the case of a 36-years-old male patient, originating from India, who presented with enlarged cervical lymph nodes and elevated liver chemistry tests. Histologically necrosing granulomas were observed in the lymph nodes, and PCR revealed DNA from *mycobacterium tuberculosis.* However, in the liver biopsy granulomatous hepatitis without central necrosis was seen. With a positive PCR for mycobacteria from liver tissue and no evidence for other hepatic diseases we started drug treatment with standard quadruple regimen consisting of isoniazid, rifampicin, ethambutol, and pyrazinamide. Five days after onset of therapy, liver chemistry tests rose 10-fold, forcing us to interrupt treatment. Gradual step-wise re-exposition with the same medication after return of liver chemistry tests to baseline was well tolerated without any further side effects. Liver involvement of tuberculosis can have many facets and may be treated by gradual dosing of standard drugs.

Key words: Granulomatous hepatitis, miliary tuberculosis, tuberculostatic drugs, liver biopsy, hepatotoxicity.

Case report

A 36-year old male patient, originating from Bombay, India, presented to the emergency department with painful swelling of a cervical lymph node, high intermittent fever up to 40°C, and elevated liver chemistry tests. The patient moved to Germany one year before. History taking revealed no history of past serious diseases. His family who still resided in India was healthy.

At presentation the patient was febrile (39.3 °C). The right part of his neck was swollen with a firm painful mass (diameter 5 cm). The swelling had occurred during the past two weeks with concomitant daily fever up to 40 °C.

Otherwise the examination of the patient was unremarkable.

Table I displays the laboratory parameters at admission and during follow-up. Initially, no major deviance was detected except for a high C-reactive protein and liver chemistry tests 2-3 times the upper normal limits. Autoantibodies, serological markers for hepatitis and angiotensin-converting enzyme (ACE) were negative or normal.

A CT scan showed enlarged cervical lymph nodes with central necrosis and several small nodules (< 5 mm) in both lungs which could not be characterized further with CT. One of the lymph nodes was explanted and histologically examined. The specimen showed granulomatous inflammation with central necrosis consistent with tuberculosis, however, no acid-fast bacteria were observed microscopically. In the meantime the patient continued to have high fever, his liver chemistry tests increased further, and he developed mild pancytopenia (*Table I*, 2 weeks after admission).

Because of the progressive nature of the disease, biopsies from liver and bone marrow were obtained. In the liver the same granulomatous inflammation was detected, but without central necrosis. The bone marrow was hypercellular without malignant cells, but acid-fast bacteria were detected microscopically. Polymerase chain reac-

Table I.

	Admission	2 weeks	4 weeks	5 weeks	6 weeks	8 weeks
AST	61	251	200	2,760	150	63
ALT	101	207	140	1,266	321	49
γ-GT	133	561	392	329	227	189
AP	133	388	421	385	252	202
WBC	7.1	2.3	3.5	4.0	2.6	3.4
Hb	143	117	131	148	129	140
Platelets	249	114	128	173	142	240

Laboratory values at admission and 2, 4, 5, 6 and 8 weeks thereafter. Treatment was started 2 days after the 4-week blood count and was stopped immediately after the 5-week blood count. AST = aspartate aminotransferase, ALT = alanine aminotransferase, γ-GT = γ-glutamyltransferase, AP = alkaline phosphatase (all in U/L). WBC = white blood count (G/L), Hb = hemoglobin (g/L), platelets (G/L).

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tion tests revealed DNA from *mycobacterium tuberculosis* in lymph node and liver samples. Treatment of miliary tuberculosis was started with a standard drug regimen consisting of 300 mg isoniazid, 600 mg rifampicin, 1.5 g ethambutol and 2.0 g pyrazinamide daily.

At day 5 of treatment, transaminases rose to values about 10 times of baseline *(Table I)*. All drugs except ethambutol were paused, and transaminases decreased rapidly. At this time cultural evidence was obtained showing mycobacteria in sputum and urine, further supporting the diagnosis of miliary tuberculosis. We awaited the spontaneous decrease of the transaminases below 4 times the upper normal limits to restart therapy by adding drugs one by one separated by 4 day-periods each. The liver chemistry tests remained constant at about 3 times the upper limit of normal with a tendency to further improvement (*Table I*, 8 weeks after admission), indicating good tolerability of the drugs upon re-introduction. The patient had no fever anymore and started to regain physical fitness.

Discussion

Tuberculosis can involve the liver to different extents producing multifarious clinical symptoms.[1] Miliary tuberculosis with liver involvement is not rare, but different presentations can obscure the origin of elevated liver chemistry tests. In our case, the appearance of the cervical lymph nodes suggested tuberculosis, but it remained unclear whether this was a localized form of the disease with elevated liver chemistry tests due to concomitant liver diseases or miliary tuberculosis with involvement of liver and bone marrow.

In our patient the liver biopsy revealed granulomas without central necrosis. A recent study demonstrated that only 5 % of hepatic granulomas without central necrosis are due to tuberculosis.[2] Isoniazid and pyrazinamide are both hepatotoxic,[3] with rifampicin increasing or inducing isoniazid hepatotoxicity. Risk factors for hepatotoxicity during antituberculotic treatment comprise younger age, Asian origin, female gender, poor nutritional status, and various genetic polymorphisms of metabolizing enzymes including cytochrome P 450 2E1, N-acetyltransferase 2 and glutathione-S-transferase M1.[4-7] Therefore, clarification of the origin of elevated liver chemistry tests was important before treatment in our patient. Since pyrazinamide-induced hepatotoxicity often has a poor prognosis,[8] administration of pyrazinamide in patients with pre-existing liver disease is not recommended. However, with liver involvement of a miliary tuberculosis quadruple treatment with four first-line drugs including pyrazinamide is desirable in order to prevent secondary resistance.

The PCR-based evidence of mycobacteria in liver tissue, the concomitant detection of acid-fast bacteria in the bone-marrow, small nodules in the pulmonal CT scan and the cultural evidence of mycobacteria in sputum and urine provided strong evidence for miliary tuberculosis with liver involvement. The initiated treatment was hampered by the extensive rise in liver chemistry tests without cholestatic involvement suggesting a hepatotoxic reaction to one or more of the used drugs. We hypothesize that in our case the basic elevation of liver enzymes including cholestatic markers (γ-GT, AP) represented the primary liver involvement during miliary tuberculosis, whereas the isolated elevation of transaminases after start of treatment mirrors the hepatotoxic reaction. Thus we considered a re-exposition with the same treatment regimen after decrease of values to baseline. The re-introduction of antituberculosis treatment after hepatotoxicity is controversial and clinical studies are rare. However, in a small prospective study from India, re-introduction of isoniazid and rifampicin was well tolerated in more than 90% of patients after resolution of drug-induced hepatitis.[9] In another small study from Turkey, gradual increase of dose and number of drugs without pyrazinamide was compared to sudden re-introduction with the same drug regimen as before hepatotoxicity, including pyrazinamide. In the latter group, 24% of patients developed hepatitis on re-introduction, while in the first group no further hepatotoxicity was recorded.[10] These results are in line with existing recommendations,[11] but these guidelines lack clear evidence from randomized trials and additional studies are warranted.

In our case, the primary treatment scheme including pyrazinamide could be re-introduced using step-by-step addition of drugs and gradual increase of dosing. This demonstrates that antituberculotic regimen including pyrazinamide can safely be employed even after hepatotoxic reactions. We speculate that immediate primary step-by-step initiation of antituberculotic treatment with liver involvement might reduce hepatotoxic reactions and should be evaluated in controlled clinical trials, but will certainly not replace regular controls of liver chemistry tests during treatment of miliary tuberculosis.

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