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Difficulties in management of tuberculous pneumonia in a patient with liver failure in the course of chronic hepatitis B and concomitant failure of the transplanted kidney

Abstract

A 62-year-old woman with liver failure in the course of chronic hepatitis B and concomitant failure of the transplanted kidney was treated for tuberculous pneumonia. The treatment was initiated with rifampin, isoniazid and pyrazinamide. Both renal and hepatic side effects required modification of this scheme. After 1 month of treatment sputum smears tested for acid-fast bacilli converted to a negative result and the chest X-ray demonstrated complete resolution of pulmonary infiltrates. Further therapy resulted in serious deterioration of the liver failure and fatal outcome.

Key words: tuberculosis, antituberculous agents, liver failure, renal failure

Introduction

A 62-year-old female was admitted on the 8th July 2003 because of the suspicion of tuberculous pneumonia. Her history included failure of the right kidney transplanted because of familial polycystic renal disease and left nephrectomy, chronic hepatitis B with cirrhosis, osteoporotic fractures of lumbar vertebrae, arterial hypertension and depression. At presentation her temperature was 38°C, blood pressure (BP) — 160/70 mm Hg; heart rate — 76 beats/min; she was moderately dyspnoeic. The chest auscultation revealed bilaterally rhonchi. The chest radiograph yielded massive diffuse infiltrates in both lungs consistent with tuberculous pneumonia (Figure 1). When the diagnosis was confirmed by positive acid-fast bacilli in sputum and bronchoalveolar lavage (BAL) the patient was administered: rifampin 600 mg/d, isoniazid 300 mg/d and pirazynamide 1500 mg/d [directly observed treatment I (DOT) regimen was not implemented due to concomitant renal and liver failure]. After 2 weeks she deteriorated with evident jaundice and laboratory signs of drug-induced hepatotoxicity (Table 1). The tuberulostatics were discontinued for five days and then reintroduced at lower doses: rifampin (450 mg/d) and isoniazid (150 mg/d) and streptomycin added — initially at 750 mg/d i.m., tailored later to

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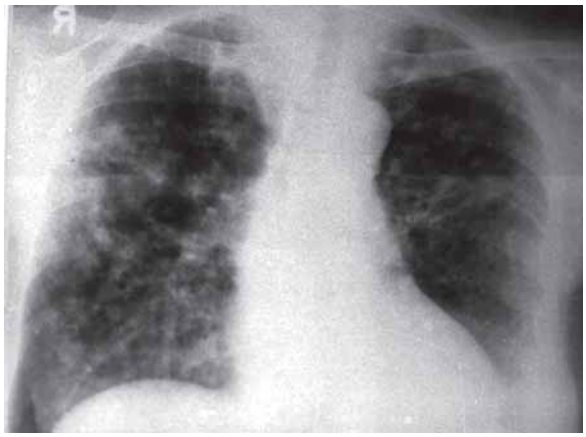

Figure 1. Bilateral diffuse pulmonary infiltrates prior to treatment

the dose 500 mg/d every second day. In the course of treatment failure of the transplanted kidney evolved (Table 1). Therefore streptomycin was discontinued and intensive supportive care instituted resulting in the normalization of renal parameters. After 1 month of treatment sputum smears for acid-fast bacilli converted to negative and radiological changes completely resolved (Figure 2). Henceforth rifampin and isoniazid were the mainstay of therapy till the 1st October 2003 when liver toxicity recurred (Table 1). Despite the discontinuation of the tuberculostatics the patient developed profuse purpuric skin eruptions, nausea and vomiting and confusion. Liver failure was the cause of patient's death on the 7th October 2003.

Table 1. Laboratory tests results: on admission, at the first liver failure exacerbation, at kidney failure exacerbation and at final fatal liver failure exacerbation

Laboratory tests	On admission 08.07.2003	First liver failure exacerbation 22.07.2003	Kidney failure exacerbation 15.08.2003	Final fatal liver failure exacerbation 01.10.2003
Heamoglobin [g/dL]	10.0	10.3	10.6	8.6
RBC * 10^9/L	3.85	3.87	3.94	3.97
Ht (%)	30.3	30.9	31.4	30.9
MCV [fl]	78.6	79.7	79.6	77.7
MCHC [g/dL]	33	33.5	33.7	27.6
MCH [pg/cell]	25	26.7	26.9	21.5
Platelets *10^9/L	145	129	–	–
Creatinine [mg/dL]	1.65	1.76	3.6	1.99
BUN [mg/dL]	40	42	140	58
ALT [U/L]	13	10	7	11
AST [U/L]	22	38	90	25
GGTP [U/L]	87	77	80	63
Total bilirubin [mg/dL]	1.28	16	6.2	14.7
AP [U/L]	194	–	–	124
pH	–	–	7.26	7.29
pCO_2 [mm Hg]	–	–	27	31
pO_2 [mm Hg]	–	–	56	57
HCO_3^- [mmol/L]	–	–	14	14
Glucose [mg/dL]	98	109	–	–
Albumin [mg/dL]	26	–	–	–
INR	1.32	–	–	1.40
APTT [s]	56	–	–	53
Potassium [mmol/L]	4.4	Not done	6.6	3.9
Sodium [mmol/L]	137	–	124	135
CMV antigen	Negative	–	–	–
CyA [μg/L]	–	–	153	282

RBC — red blood cells; Ht — hematocrite; MCV — mean cell volume; MCHC — mean corpuscular hemoglobin concentration; MCH — mean corpuscular hemoglobin; BUN — blood urea nitrogen; ALT — alanine aminotransferase; AST — aspartate aminotransferase; GGTP — γ-glutamyl transpeptidase; AP — alkaline phosphatase; P — pressure; INR — international normalized ratio; APTT — activated partial thromboplastin time; CMV — cytomegalovirus; CyA — cyclosporine A

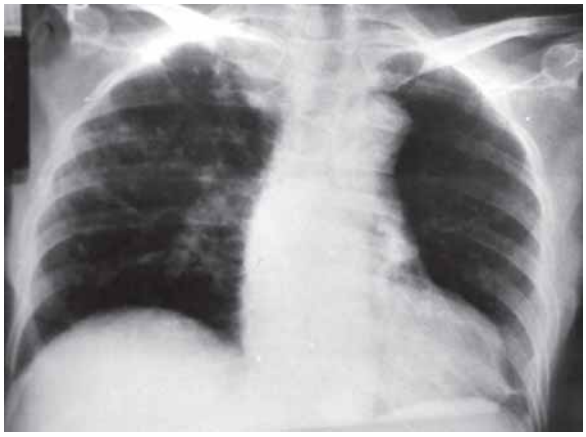

Figure 2. Resolution of pulmonary infiltrates in the course of treatment

Discussion

Tuberculosis in kidney transplant patients and/or concomitant liver failure is a serious and relatively frequent clinical problem [1].

Despite the potentially effective therapeutic options tuberculosis is still one of the main causes of morbidity due to infectious diseases. The World Health Organization (WHO) provides treatment standards for most clinical courses of tuberculosis but in rare cases corrections of recommended schemes are needed. It includes intolerance or drug resistance and concomitant diseases: HIV infection, renal and liver failure [2].

In the presented case there were a number of unfavorable factors that influenced the outcome of the treatment. Most of the antituberculous agents have hepatotoxic and nephrotoxic potential [3]. Rifampin, isoniazid and pirazinamide are contraindicated in liver failure which warrants the use of drugs excreted by the kidneys. On the contrary, in the setting of renal failure rifampin, isoniazid and pirazinamide are administered at normal doses but streptomycin and ethambutol are avoided. Our patient had initially debilitated liver function and failure of the transplanted kidney, which considerably limited the choice of drugs. The degree of the pulmonary infiltrate, clinical condition and attempt to avoid the development of drug resistance determined the use of multidrug regimen involving pirazinamide which is active in acidic environment of caseous necrosis.

An additional complicating factor was immunosuppressive treatment with Cyclosporine A (CyA), which predisposes to opportunistic infections including tuberculosis as well as impairs the renal function. Both CyA and rifampin are metabolized in li-ver. Additionally rifampin lowers serum concentration of CyA rendering it necessary to monitor CyA serum level during antituberculous treatment [4]. In the presented case CyA levels were maintained within therapeutic values. Moreover the patient was on lamivudine to treat chronic hepatitis B. This drug is excreted by the kidneys, which under the condition of renal failure necessitates the modification of its dosage and may influence excretion of other medications such as streptomycin. Therefore the doses of streptomycin were corrected. Despite this approach liver and kidney insufficiency ensued. Modifications of drug regimen: decreasing the doses and decreasing the frequency of drug administration did not succeed. During the treatment there was aggravating jaundice with increased liver function tests [total bilirubin (T. Bil.), alkaline phosphatase (AP), γ-glutamyl transpeptidase (GGTP)] without aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation which was the consequence of liver cirrhosis [5]. Finally, irreversible liver failure eventuated leading to the patient's death. Worsening of renal insufficiency turned out to be a se-condary unfavorable factor. The low compliance, depre-ssion and bed regimen due to compressive fractures of lumbar vertebrae further complicated the treatment and rehabilitation. The patient also poorly tole-rated analgetic treatment with analgesics — intolerance of trama-dol and non-steroidal anti-inflammatory drugs (NSAIDs), 24-hour confusion after administration of morphine (10 mg/d). Despite the intermittent and incomplete treatment a significant remission of tuberculosis was achieved.

Conclusions

Severe renal and liver failure is a potential risk for life-threatening side effects during treatment, thus health hazard should be thoroughly disscussed also with the patient and his family.

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