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Regression of alveolar echinococcosis after chronic viral hepatitis C treatment with pegylated interferon alpha 2a

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Summary

We present a case of 53 years old patient with transplanted kidney, chronic hepatitis C and alveolar echinococcosis who was treated with pegylated interferon α which resulted in regression and calcification of *Echinococcus multilocularis* loculi. Patient had been diagnosed with chronic hepatitis C two years after kidney transplantation. Hepatitis was left untreated because of immunosuppressive treatment and satisfactory graft function. Nine years after transplantation the patient was diagnosed with alveolar echinococcosis and treated with mebendazole 2 x 200 mg daily for 6 months. Cessation of temporary treatment resulted in echinococcosis progression with appearance of secondary loculi and a small ascites after which mebendazole was restarted. Ten years after transplantation, kidney graft failure occurred and the patient was started on hemodialysis in conjunction with pegylated-interferon alpha 2a for treatment of chronic viral hepatitis C. Complete early viral response was observed 3 months after therapy initiation while a follow-up CT scan after 4 months did not document any changes in the number or size of *E. multilocularis* loculi. A completed course of antiviral therapy resulted in sustained viral response while a subsequent second follow-up CT scan 6 months after cessation of antiviral therapy documented regression and calcification of main *E. multilocularis* loculi along with resolution of secondary loculi and ascites.

Keywords: alveolar echinococcosis; chronic hepatitis C; pegylated-interferon; PEG-IFN; mebendazole; liver echinococcosis regression; sustained viral response

Introduction

Alveolar echinococcosis is a sporadic infection restricted to the northern hemisphere. Central Europe is an endemic area for *Echinococcus multilocularis* (Kern *et al*., 2011). A recent Swiss report identified the incidence of alveolar echinococcosis at 0.26 cases per 100 000 annually (Schweiger, 2007). In Slovakia, the first *E. multilocularis* infection in animal was described in 1999 (Dubinský *et al*., 1999), with first animal-to-human transmission described in 2000 (Kinčeková *et al*., 2001). To date, eleven patients have been diagnosed with alveolar echinococcosis in Slovakia while the detection in foxes stands at nearly two thirds of its population (Miterpáková *et al*., 2006).

The most common localization of *E. multilocularis* infection is the liver followed by lungs. Alveolar echinococcosis is a life-threatening disease. It can metastasize to remote organs, with the most dangerous localization of secondary focuses in the brain. Surgery, complementary chemotherapy along with mebendazol/albendazole is the preferred treatment option. Untreated alveolar echinococcosis exceeds 90 % mortality, while the survival rate with treatment in a 5 year period stands at 88 % (Kern *et al*., 2011; Bresson-Hadni *et al*., 2000).

In this paper we describe the case of a 53 year old male with chronic viral hepatitis C, dialysed due to kidney graft failure, which developed alveolar echinococcosis and was treated with pegylated-interferon (PEG-IFN) alpha 2a.

Case report

Patient, born in 1956, following the kidney transplantation from deceased donor was admitted to the hospital with fever and progressive abdominal pain (Dražilová *et al*., 2011). The patient was diagnosed with chronic hepatitis C genotype 1, histology grade 1, stage 2 seven years before admission. Graft function in posttransplant period was stable and optimal, the patient was treated with standard maintenance immunosupresive protocol (cyclosporine A, mycophenolate mofetil and low-dose prednison), metylprednisolon bolus therapy (1 g/m^2 body surface area), was administered two months prior to admission due to

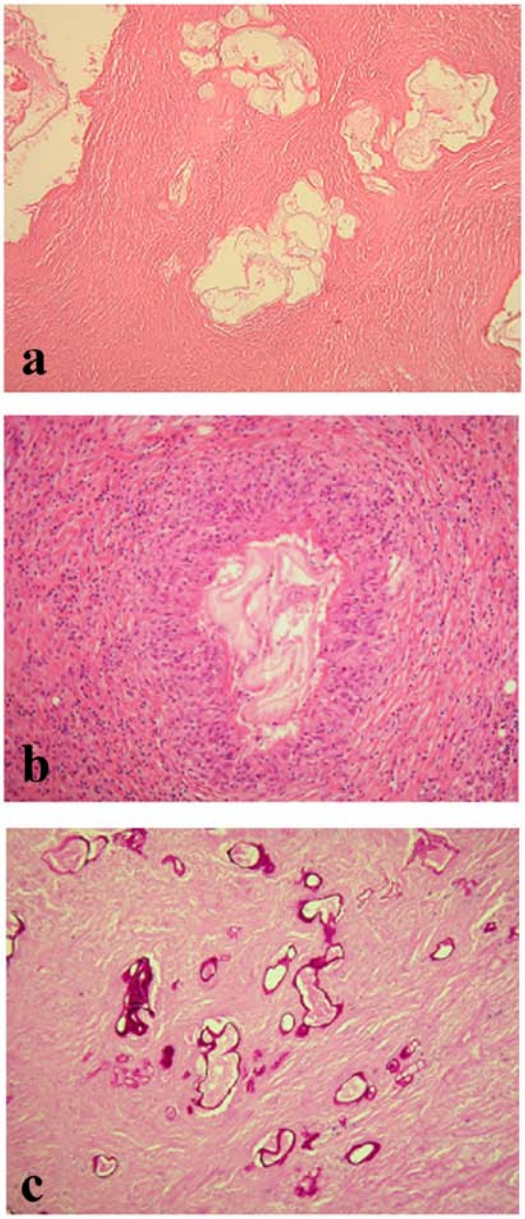

Fig. 1. Alveolar echinococcosis – histological findings. Alveoli of different sizes embedded in fibrous tissue – Haematoxylin and eosin (1a); granulomatous reaction and inflammatory infiltrate containing many eosinophils and neutrophils – Haematoxylin and eosin (1b); membranes stained with period acid-Schiff with diastase (1c)

creeping creatinine (suspection of acute rejection was not confirmed by biopsy). Empiric antibiotic treatment due to febrile status was ineffective. Abdominal ultrasound and computer tomography (CT) scan revealed three tumorous lesions in the liver, radical surgical intervention was not executable. Histological examination of the tissue from the lesions demostrated alveolar echinococcosis (Fig. 1), serology for *Echinoccocus multilocularis* was positive. Long-term treatment by mebendazole 200 mg twice daily led to disappearance of the clinical symptoms. Mebendazole dose was reduced due to liver and kidney insuficuciency. After the therapy cessation patient was again hospitalized with fever and progression of cystic lesions in CT scan. At the time small ascites transiently appeared. Following the mebendazole therapy reinstalation the clinical course of echinococcosis was improved and remained stable, transplant kidney failure occurred due to progression of interstitial fibrosis/tubular atrophy and chronic haemodialysis was initiated one year later (Dražilová *et al*., 2011). Patient is treated by mebendazole indefinitely.

In February 2009 regular dialysis was started; blood urea nitrogen: 28.3 mmol/l, creatininemia: 465 µmol/l, glomerular filtration: 0.14 ml/s. In our opinion, transplant kidney failure was caused by progression of interstitial fibrosis/tubular atrophy of the graft and was unrelated to *E. multilocularis* infection or its therapy. Repeated CT before treatment with PEG IFN on Fig. 2a showed hypodense focus in S8 with diameter of 96mm (solid arrow), on Fig. 2b other focuses in segments 4 and 6 with diameter of 90 mm and 85 mm respectively (solid arrow). Secondary smaller focuses are also visible (dashed arrow).

The patient was treated with PEG-IFN alpha 2a in monotherapy from February 2009 for chronic viral hepatitis C after kidney graft failure occurred and he was started on dialysis. Viral load before therapy was 129 630 ME/ml (350 000 copies per ml) (Cobas Amplicor, Roche). Activity of hepatic transaminases and cholestatic enzymes was not elevated. First assessment of antiviral treatment efficacy in 12th week revealed complete early viral response

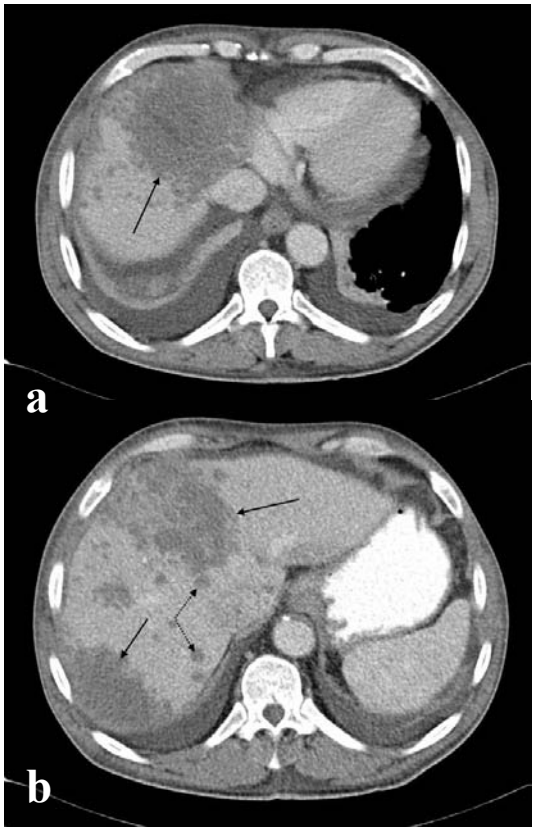

Fig. 2. CT scan before PEG IFN treatment. 2a: Hypodense focus in S8 with diameter of 96mm (solid arrow), 2b: focuses in segments 4 and 6 with diameter of 90 mm and 85 mm respectively (solid arrow). Secondary smaller focuses are also visible (dashed arrow).

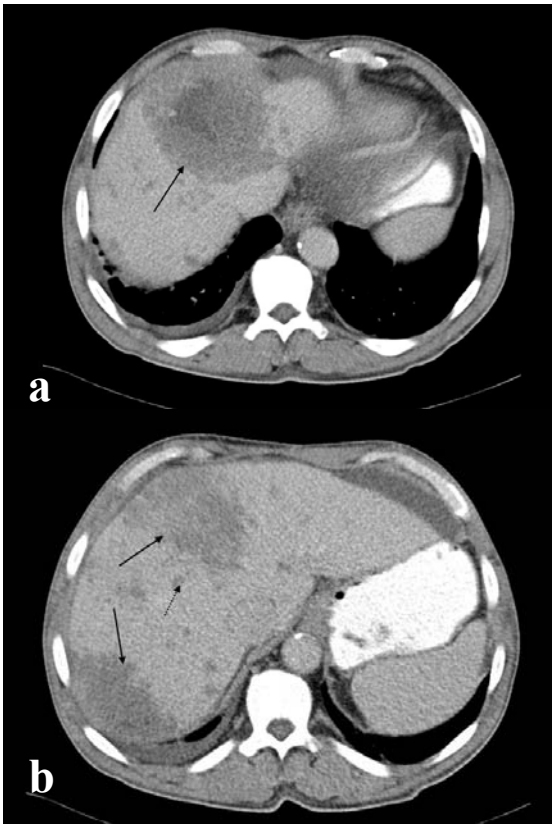

Fig. 3. CT scan after 4 months of PEG IFN treatment. Hypodense focus in segment 8 with diameter 98 mm (fig. 3a) and focuses in segment 4 and 6 with diameters of 85 mm (fig. 3b – solid arrows). Secondary focuses (dashed arrows).

(quantitative HCV RNA was negative). Follow-up CT scan after 4 months of PEG-IFN treatment documented no change in size, appearance or number of *Echinococcus* loculi, hypodense focus in segment 8 with diameter 98 mm (Fig. 3a) and focuses in segment 4 and 6 with diameters of 85 mm (Fig. 3b – solid arrows). Secondary focuses (dashed arrows) also persisted.

In total, PEG-IFN alpha 2a treatment was 48 weeks long without interruptions. No serious adverse effects were observed. Minor side effects included flu-like syndrome and dyspepsia in the beginning of the treatment course and low-grade trombocytopenia and neutropenia later on. During treatment the patient received concomitant immunosuppression with tacrolimus which was changed to cyclosporine A, which was later discontinued. Following the completed course of PEG-IFN alpha 2a treatment, and 24 weeks after treatment cessation, HCV RNA qualitative test (Cobas Amplicor, Roche) was negative. The patient achieved sustained viral response. A 6 month follow-up CT scan, post-PEG alpha 2a treatment cessation, identified regression of primary *E. multilocularis* focus in S8 with the creation of calcified margins (Fig. 4a, solid arrow). Regression of other focuses in S4 and S6 were observed (Fig. 4b, solid arrows).

Discussion

Here we report the case of a 53 year old patient, receiving hemodialysis due to renal failure in a transplanted kidney that was treated with PEG-IFN alpha 2a for chronic viral hepatitis C. He was diagnosed with alveolar echinococcosis 18 months earlier. Treatment with PEG-IFN alpha2a in conjunction with mebendazole chemotherapy led to the regression of alveolar echinococcosis in the liver.

The chemotherapy of alveolar echinococcosis with available anthelmintics (benzimidazoles) has only the parasitostatic effect. Moreover, the results of treatment may be affected by immunological status of the host, host susceptibility and the actual stage of infection. The dominance of Th1 response is important in defensive reactions of a host infected with *E. multilocularis*. Sufficient published data suggest that IFN modulates host immune response in infected patients. Th-2 type immune response with anti-inflammatory cytokines secretion (IL-4, IL-5, IL-13) leads to disease progression as opposed to cell-mediated Th-1 type response which leads to necrosis (Vuitton & Gottstein, 2010). Emery *et al*. (1997) infected A/J and BALB/c mice by intrahepatic inoculation of a metacestode homogenate. 13 weeks after infection, the mean metastatic burden of

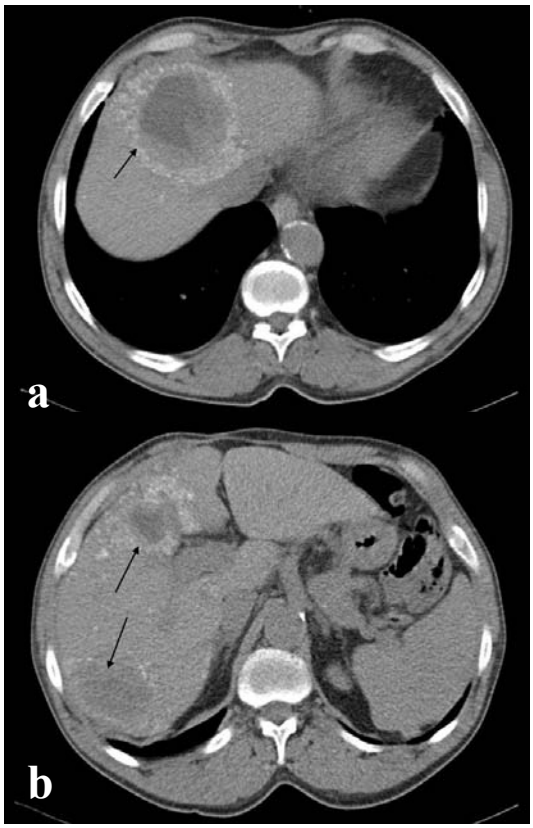

Fig. 4. CT scan 6 months after cessation of PEG IFN treatment. Regression of primary Echinococcus focus in S8 with the creation of calcified margins (Fig. 4a, solid arrow). Regression of other focuses in S4 and S6 were observed (Fig. 4b, solid arrows).

A/J mice was significantly lower than that of BALB/c mice. Moreover, at this time, some BALB/c mice spontaneously died from their infection whereas all A/J mice remained in good health. The relative resistance of A/J mice to parasite development was associated with a high parasite-induced production of IFN-gamma and IL-2. These data suggest that elevated IFN-gamma results in a more benign course of the infection.

Antiparasitic chemotherapy also stimulates IFN-gamma secretion while elevated IFN-gamma levels increase the effectiveness of antiparasitic chemotherapy (Borošková *et al*., 2003). Dvorožňáková *et al*. (2004) treated mice infected with *Echinococcus multilocularis* by free or liposomized albendazole. Besides identifying the effect on cyst growth, the authors observed that only moderate IFN-gamma elevation was detected after treatment with free albendazole, however, a profound increase of its concentration was observed shortly after administration of liposomized albendazole.

Rigano *et al*. (1995) studied the relation of IFN-gamma production to the effectiveness of pharmacological treatment in human hydatid disease. After parasite antigen stimulation, peripheral blood mononuclear cells (PBMC) from full responders produced significantly more IFN-gamma than PBMC from non-responders. PBMC from partial and low responders produced intermediate cytokine concentrations.

Discussed data suggest that IFN could be beneficial in the treatment of *E. multilocularis* infection. Liance *et al*. (1998) showed that the treatment with IFN-gamma, 1 microgram per day twice a week, transiently reduced the liver metacestode load and the metastasis weight as far as 6 weeks after the end of 3 week treatment and slightly increased Th1-type T cell response. In contrast, the treatment with IFN-gamma 5 micrograms daily twice a week increased the liver metacestode load. Godot *et al*. (2003) analysed the effects of recombinant IFN alpha-2a in the susceptible C57BL/6J *Echinococcus multilocularis* infected mice. After 90 days post-infection, 75% of infected IFN alpha-2a-treated mice had no hepatic lesions and half were fully protected. IFN alpha-2a treatment markedly decreased the abnormally elevated production of IL-10 in both spleen cell cultures and peritoneal macrophage cultures from infected mice while restoring phagocytosis and oxidative metabolism of macrophages. It also inhibited IL-6 and IL-13 antigen-induced secretions in spleen cell cultures.

Jenne *et al*. (1998) reported a case of a 61 year old patient with *Echinococus multilocularis* infection of the lungs, liver, pericardium, bones and brain, which relapsed after 19 years of antiparasitic chemotherapy. This patient received 16 cycles of recombinant IFN-gamma; in total 250 µg monthly for 16 months. There were no serious adverse effects, beside initial flu like syndrome. Treatment lead to symptomatic relief, moreover, none of the abdominal or thoracic lesions had increased in size, nor were newer lesions observed.

A new approaches to the therapy of alveolar echinococcosis offer the use of immunomodulators because the result of benzimidazole's therapy is complicated with patient's immunosuppression caused by *E. multilocularis* metacestode. The use of cytokine IFN-g or IL-12 in combination with benzimidazole stopped the progression of disease or reduced the growth of metacestode (Vuitton *et al*., 2006) suggesting its usefulness in therapy. However, the using of recombinant cytokines in therapy is technically and financially demanding. Therefore new ways to support a secretion of endogenous cytokines in patients are searched. Results of alternative therapeutical strategies with use of immunomodulators (Dvorožňáková *et al*. 2008, 2009; Porubcová *et al.,* 2007) contributed to higher efficacy of the anti-echinococcus treatment. Our patient with alveolar echinococcosis has suffered from chronic hepatitis C. The golden standard of the chronic hepatitis C treatment is combined therapy with PEG-IFN and ribavirin, but in patients treated by haemodialysis PEG-IFN monotherapy is preferred (EASL, 2011). In our case report we did not administer the PEG-IFN treatment with ribavirin during the period of functioning kidney graft as it is widely acknowledged that the treatment of chronic hepatitis C with IFN in patients, with transplanted kidneys, can lead to the acute kidney graft rejection (Wéclawiack *et al*., 2008). Treatment with PEG-IFN alpha-2a was indicated following the kidney graft failure and after the beginning of regular dialysis in our patient. The patient received 180 mcg of PEG-IFN alpha 2a weekly for 48 weeks in combination with mebendazole 200 mg b.i.d. Follow-up CT, 6 months after the end of PEG-IFN alpha 2a treatment, documented significant size reduction of primary *Echinococcus* loculi, complete resolution of secondary loculi and ascites. Furthermore, primary lesions developed a progressively increasing calcified rim, which suggest inactivity of the cysts (Eckert *et al*., 2001).

Conclusion

The presented case report suggests that PEG-IFN alpha 2a treatment in conjunction with standard antiparasitic therapy could lead to regression and calcification of *Echinococcus multilocularis* lesions in the liver. This information presents a viable treatment alternative in patients with contraindications to surgery. However, high cost of interferon treatment is a significant limitation of this treatment modality.

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