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Letter to the Editor

Cerebral cystic echinococcosis reactivation during therapy for squamous tumor of the cervix: possible interactions?

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Dear Editor,

Human echinococcosis is a zoonotic disease related to infection by the *Echinococcus* spp., tapeworm parasites [1]. Most cases of the disease in Europe are related to *Echinococcus granulosus sensu lato (s. l.)*, and human infection is widespread and considered a significant public health issue in countries where dogs, the main definitive hosts, live in close contact with humans and livestock [2,3]. Organ involvement in Cystic echinococcosis (CE) mainly implicates the liver (about 70-80%) and secondly lungs (20%), on the other hand, cerebral CE is epidemiologically uncommon and occurs in 2% of CE [1-3]. Immunosuppression may impact the development of *Echinococcus* spp. infections in experimental hosts, transplanted patients, and individuals with AIDS [4,5]. In addition, patients receiving immunosuppressive therapy for malignant and inflammatory disorders have also been documented to have accelerated growth of *Echinococcus* spp. metacestodes [6,7].

Recently, a 43-year-old Caucasian woman presented to the emergency department after one week of confusion, ideomotor slowdown, and nystagmus. Her physical examination was otherwise clear. She had just completed the second cycle of chemotherapy with cisplatin, paclitaxel, and bevacizumab for a squamous tumor of the cervix. A magnetic resonance imaging (MRI) of the brain revealed multiple cystic encephalic lesions (Figure 1). The cysts were hypo- to iso-intense on T1 and DWI, and hyperintense on T2, after contrast administration, peripheral rim enhancement was revealed, a typical sign of parasitic disease. The results of serological tests (immunoblot diagnostic assay, LDBIO Diagnostics, Lyon, France) revealed an isolated high titer antibody for *Echinococcus* spp. 1:640, with a profile on immunoblot typical for *E. granulosus s.l.* marked by a 7 kDa plus large diffuse 17 kDa bands. Total body computed tomography was negative for other cysts. A brain biopsy was not undertaken due to the high risk of the procedure. A radiological and serological diagnosis of cerebral CE was made. Surgery is the treatment of choice along with benzimidazoles. Nevertheless, the patient had no surgical indications and was treated with albendazole. The hydatid cysts began to shrink in diameter after two weeks of treatment and neurological symptoms have gradually improved. The prognosis remains critical for the lack of complete surgical eradication of cysts.

Currently, there are several reports on the presence of echinococcosis in patients with cancer, despite cerebral echinococcosis, due to the reactivation of *Echinococcus* spp. metacestodes during malignancy- and chemotherapy-related immunosuppression is still uncommon.

Immunity is implicated in the eradication and in promotion of both cancer and echinococcosis [8]. Immune modulation may be considered a critical factor influencing the course and severity of the parasitic disease. In fact, *Echinococcus* spp. could use two main mechanisms to subvert the host immune response: passive escape, in which the parasite, by developing into a larval form, avoids the damaging effects of an immune response, and immunomodulation, through which the parasite actively interacts with the host immune system to reduce the impact of a host response [8].

Moreover, the exact relationship between *E. granulosus s.l.* and cancer has long been unclear until the last decade, when an epidemiological study on patients with CE occasionally found a negative correlation between CE and solid tumors [9]. This extraordinary phenomenon, although still in debate, has led to the hypothesis that CE may elicit a protective effect against cancer. Subsequently, results from studies carried out by different research groups have supported this hypothesis [10–12].

Coexistence of *E. granulosus s.l.* infection and cancer have been broadly reported, such as coexistence with hepatocellular carcinoma, lung carcinosarcoma, liver mucinous cystadenoma, renal sarcoma, renal adenocarcinoma, or ovarian epithelial tumor and lymphoepithelioma-like gastric carcinoma [5,6]. Up to now, to our knowledge, no coexistence or reactivation in patients affected by cervix cancer has ever been published. Nevertheless, it is well known that an increased incidence of alveolar echinococcosis (AE) in immunosuppressed patients and immunocompromised patients accounts for 18-31% of the newly diagnosed AE cases in Europe [5,6].

The rapid and devastating reactivation after the end of the second cycle of chemotherapy could be related to the profound immunosuppression due to the underlying disease and chemotherapy-related immunomodulation. Moreover, hypothetical role to slow down initially the reactivation was done by taxanes. Pensel *et al.* have described that paclitaxel (PTX), at clinically achievable concentrations, inhibits in vitro the survival of larval form, protoscoleces and metacestodes of *Echinococcus granulosus s.l.* [13]. Data on PTX were also confirmed by Huang *et al.* that their study found that paclitaxel

Figure 2. hypothetic activity of anti-cancer agents against Echinococcus before the reactivation of cerebral lesions

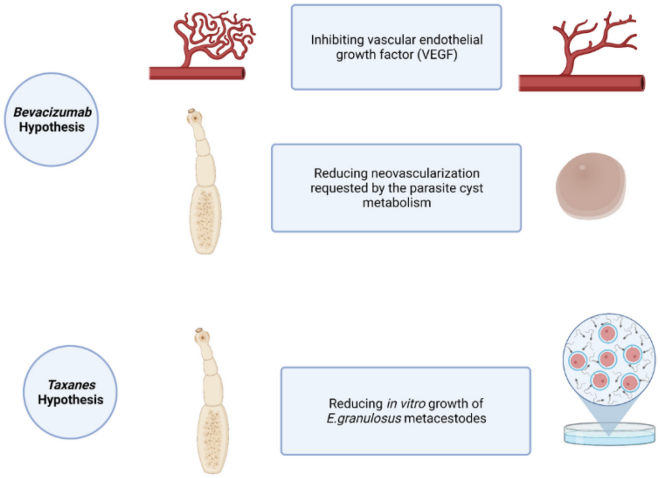
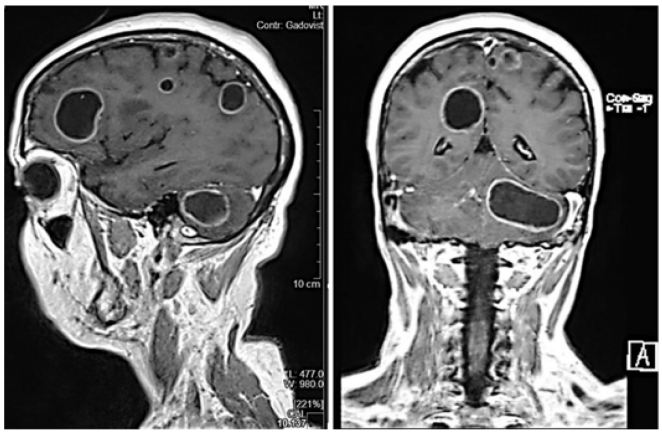


Figure 1. magnetic resonance imaging of cerebral cystic echinococcosis. A magnetic resonance imaging (MRI) of the brain revealed multiple cystic encephalic lesions. The cysts were hypo- to iso-intense on T1 and DWI and hyperintense on T2. After contrast administration, peripheral rim enhancement was revealed on the MRI.



inhibited in vivo and in vitro metacestodes of *E. multilocularis* growth and proliferation [14] (Figure 2).

Moreover, recent findings on the life cycle of *Echinococcus* spp. showed the suppression of angiogenesis by different molecules (i.e., anacardic acid) in the metacestodes through inhibiting vascular endothelial growth factor (VEGF)-induced signaling pathways [15]. In addition, Matera *et al.* found higher levels of VEGF in CE patients possibly associated with neovascularization requested by the parasite cyst metabolism [16]. In our case, chemotherapeutic regimen comprised bevacizumab which is one of the most active of the wider used anti-VEGF targeted therapy. We hypothesize that also anti-VEGF activity of bevacizumab on cancer cells could modulate tapeworms growing (Figure 2).

In conclusion, interplay between cancer and echinococcosis is an interesting and still little-known field of research in infectious diseases. Clinicians should be aware to rule out echinococcosis in previously reported compatible lesions or new cystic lesions occurring in immunosuppressed patients.

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