

Case Report

Alveolar echinococcosis of the liver with a rare infiltration of the adrenal gland

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Summary

Human alveolar echinococcosis (AE) is a silently-progressing disorder that has become a threat in many countries. Since 2000, when the first case was recorded, the number of human AE patients in Slovakia is on continuous raise. The article presents a rare case of alveolar echinococcosis with infiltration in the adrenal gland and discusses the problems associated with differential diagnosis of the disease. In 2016, abdominal ultrasound performed due abdominal pain complaint showed the presence of cystic lesions in the right liver lobe of 54-year old female patient. During surgery, another lesion in the right adrenal gland was found, and neoplastic processes or echinococcosis were considered in the differential diagnosis. Due to unclear correlation between radiology, serology and histopathology results and endemic situation in Slovakia, molecular examination was recommended. Subsequently *E. multilocularis* was confirmed as etiological agent of infection. Alveolar echinococcosis is considered as a rare disease, with very few patients referred to clinicians or hospitals that sometimes have almost none existing experience with the diagnosis and treatment of the disease. Therefore, the establishment of networks or reference centres specialized on management of the disease would be suitable way to provide the patients with the best care and improve the disease diagnosis, treatment and prognosis.

Keywords: Alveolar echinococcosis; *Echinococcus multilocularis*; Diagnosis; Adrenal gland

Introduction

Human alveolar echinococcosis (AE) is a life-threatening parasitic disease caused by larval stage (metacestode) of the fox tapeworm, *Echinococcus multilocularis*. It is an important zoonotic parasite, widely distributed in the northern hemisphere that predominantly circulates in wildlife within carnivores (foxes, wolves, raccoon dogs, jackals) as definitive host and different species of small mammals as intermediate hosts (Eckert & Deplazes, 2004; Romig *et al.*, 2017). Human infection occurs after the accidental ingestion of the infective parasite eggs from contaminated envi-

ronment. Without careful clinical management, the disease has a poor prognosis and can result in the death of an infected patient within 10 to 15 years (Eckert & Deplazes, 2004). The liver is the most often affected organ and the parasite shows features similar to malignant tumours with local invasive and infiltrative growth and metastasis formation (Brunetti *et al.*, 2012; Gottstein *et al.*, 2015a). Several types of complications may occur in affected patients. Among many others those include biliary obstruction, septicaemia due to repeated cholangitis, bacterial infection of necrotic cavities in the lesion and portal hypertension (Brunetti *et al.*, 2010; Piarroux *et al.*, 2011; Gottstein *et al.*, 2015b).

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In the last two decades, increased incidence of AE and prevalence of *E. multilocularis* in some European countries, e.g. in Switzerland, parts of France, Germany and Austria, and its significant expansion into the Northern, Eastern and Western Europe have been documented. Moreover, the endemicity of the parasite in fox populations of Baltic States, Poland, Slovakia, Romania, and Slovenia and the increase in incidence of human AE cases have been confirmed (Combes *et al.*, 2012; Wahlström *et al.*, 2012; Marcinkuté *et al.*, 2015; Gottstein *et al.*, 2015b) pointing out on the relevance of the issue. The correct diagnostic and therapeutic approach is crucial to improve the prognosis of patients and prolong their survival rate. The article presents a rare case of alveolar echinococcosis with infiltration to the right adrenal gland and discusses differential diagnosis of the disease.

Case Presentation

A 54-year old female patient without any pre-symptomatic period had been monitored since 2012 for a mild hepatomegaly and liver steatosis. In 2016, abdominal pain under the right costal margin appeared. Abdominal ultrasound revealed the presence of cystic lesions in the right liver lobe. Subsequent computed tomography confirmed the proliferation of lesions into the S5 and S8 liver segments and the presence of smaller cyst on the periphery of lesion (Fig. 1). For differential diagnosis a neoplastic process and echinococcosis were considered. Serological ELISA examinations for the presence of antibodies to *Echinococcus* spp. using *E. granulosus* antigen B (AgB) and *E. multilocularis* somatic antigen were performed according to Reiterová *et al.* (2014). The results confirmed

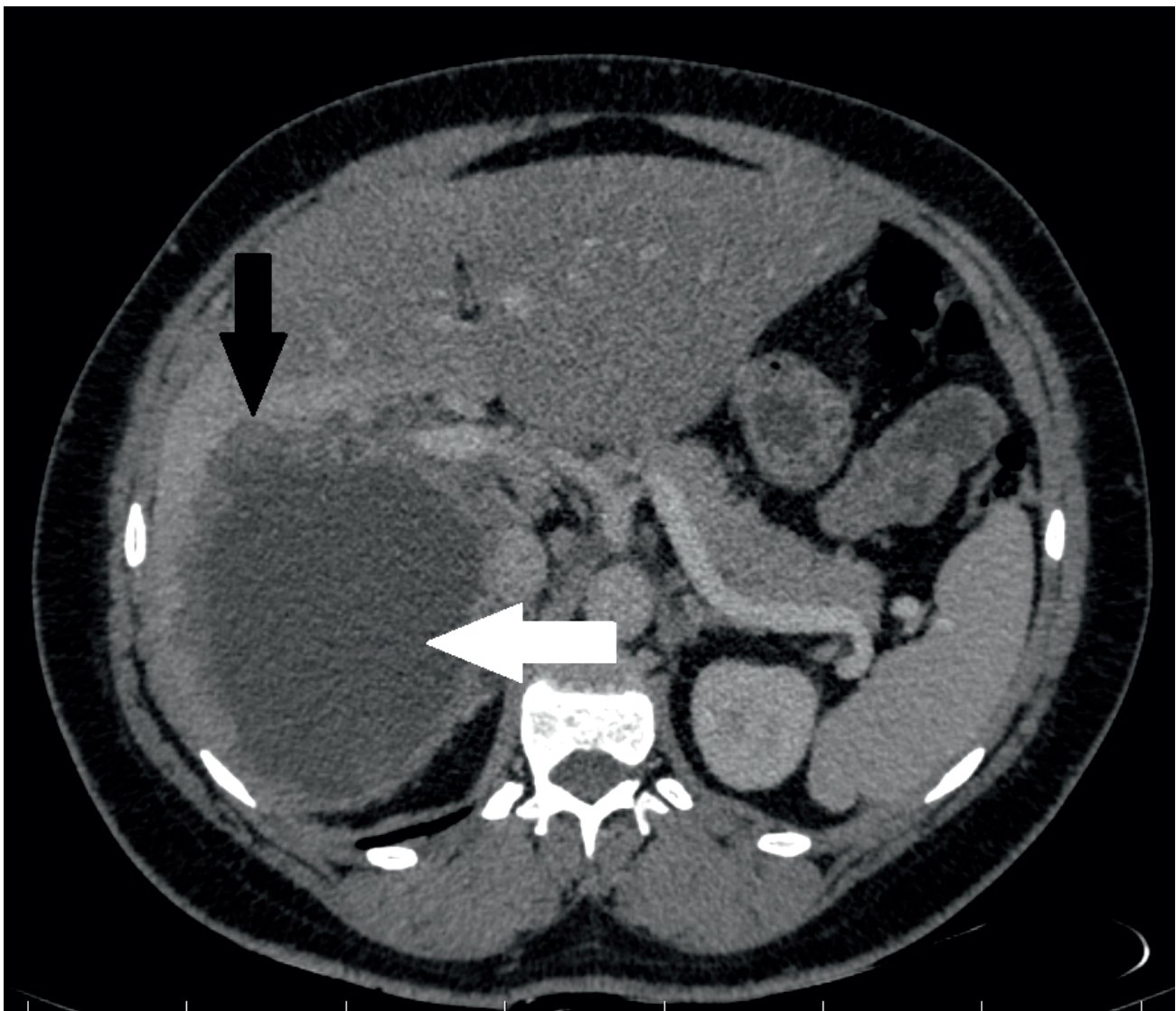


Fig. 1. Computed tomography. Axial image of the abdomen. White arrow shows extensive infiltration of right liver lobe (white arrow) and smaller (daughter) cyst on its periphery (black arrow).

the presence of high antibody titres of antibodies to *E. granulosus* and medium antibody titres to *E. multilocularis*. Consequently, the chemotherapy with albendazole was initiated and radical surgical resection to reduce the parasitic mass was recommended. During the extensive hepatectomy of the right liver lobe (S5 – S8 segments) an infiltration in a right adrenal gland (Fig. 2) was identified. Therefore a right-side adrenalectomy was also performed. Results of histopathological examination on biopsy material indicated cystic echinococcosis. However, due to unclear radiologist image interpretation, histopathological diagnosis and serological results as well as endemic situation in Slovakia, the molecular examination was recommended. After the DNA isolation utilising QIAGEN DNeasy Blood & Tissue Kit (Hilden, Germany), the PCR amplification of mitochondrial *nad1* gene was performed with specific *E. multilocularis* primer pair according to Schneider *et al.* (2008) with

positive result. Subsequent Sanger Sequencing of amplification product confirmed *E. multilocularis* as etiological agent of infection and the diagnosis of alveolar echinococcosis with the secondary infiltration to right adrenal gland was confirmed. Currently, the patient is followed up at the Clinic of Infectology and treated by albendazole.

Ethical Statement and/or Informed Consent

The patient agreed with all examinations and publication of case report and signed the informed content. No identifying data are presented in the paper. Study was performed in accordance with the ethical standards as laid down in the Declaration of Helsinki of 1975, as revised 2013.

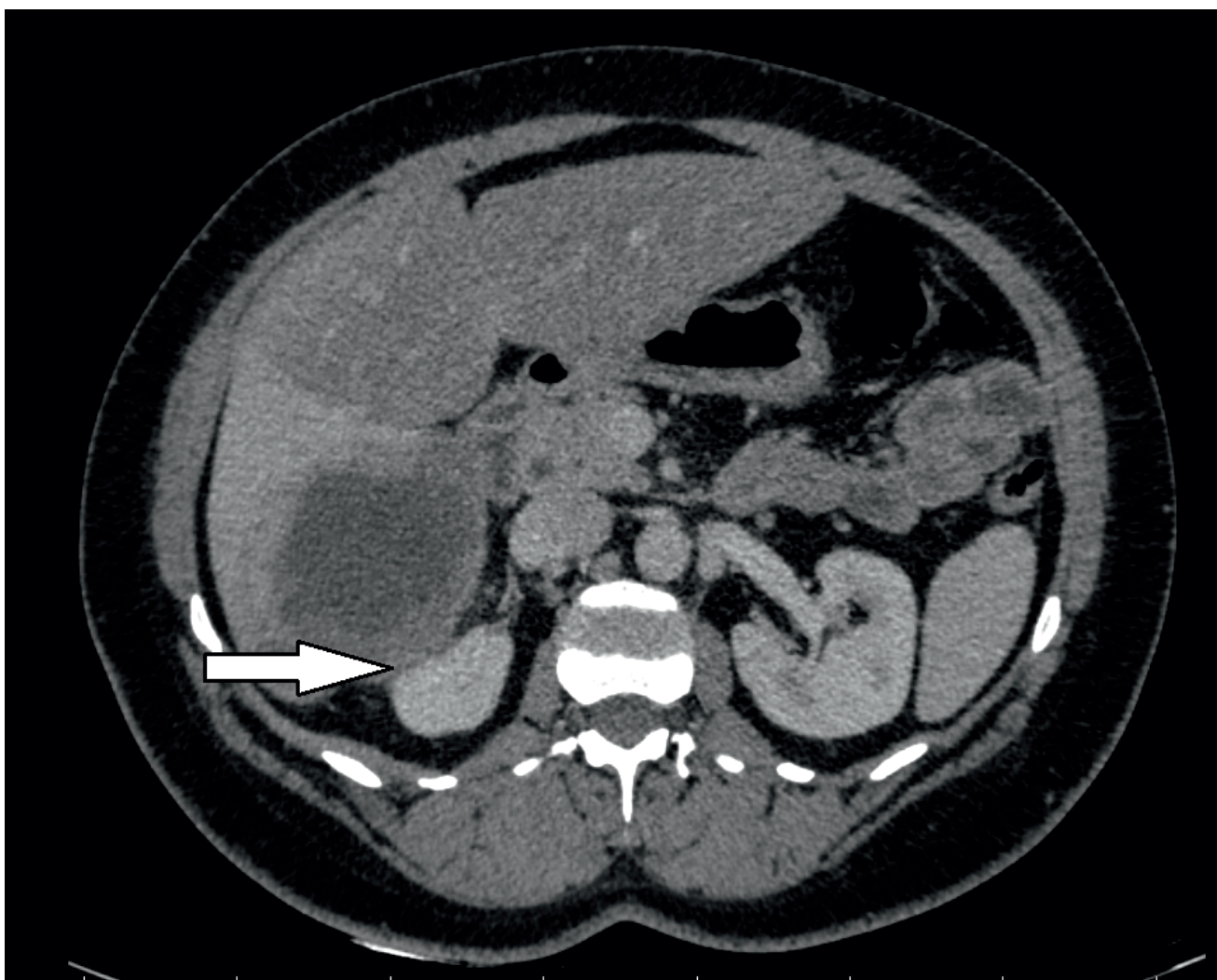


Fig. 2. Computed tomography. Axial image of the abdomen. Infiltration of right adrenal gland (white arrow).

Discussion

Human alveolar echinococcosis is a silently-progressing hepatic disorder that has become a threat in many countries. In Slovakia, as well as in majority of European countries, the expanding red fox populations and their urbanisation are underlying factors that increase the infection risk for humans (Hegglin *et al.*, 2015; Liccioli *et al.*, 2015; Marcinkutė *et al.*, 2015). In Slovakia, since 2000 when the first case was recorded, the number of human AE patients is on continuous raise (Antolová *et al.*, 2020).

Larval stage of *E. multilocularis* usually proliferates in affected organ (most often liver) as a multivesicular structure that may involve several liver segments, which expand along liver vessels and biliary tract, and finally infiltrate neighbouring organs (Kern *et al.*, 2006).

The disease has no pathognomonic clinical signs and its preliminary diagnosis often depends on the results of imaging methods and serological examinations. Regarding differential diagnosis, especially when more or less accidental detection of liver lesions are confirmed, the neoplasms, focal hepatic lesions and abscesses are often considered. The most frequent AE morphological profile is characterized by intrahepatic heterogeneous, infiltrative mass with irregular outlines and necrotic centre that appear on ultrasound as hypoechoic and hyperechoic lesions (Reuter *et al.*, 2001; Vuitton & Bresson-Hadni, 2014). Serological ELISA examination is a method of choice to confirm the presence of specific antibodies to *Echinococcus* spp., often followed by more specific Western blot. However, due to cross reactivity between *E. multilocularis* and *E. granulosus* and some other parasitic species and occasionally the absence of specific antibodies production in approximately 5 % of patients (Eckert & Deplazes, 2004; Fecková *et al.*, 2020) the results of serology may be contradictory. Therefore, to confirm the diagnosis, a histopathological examination or detection of parasite-specific DNA should be also performed (Kern, 2010). Histologically, lesions are characterized by the parasitic germinal layer surrounded by acellular laminated layer. Next layers are formed by epithelium-like macrophages, concentric layers of immune response cells (macrophages, lymphocytes, and eosinophils), cells involved in fibrosis development, collagen bundles and various components of extracellular matrix (Reuter *et al.*, 2001; Vuitton & Bresson-Hadni, 2014).

In presented case, the conclusion of radiologist was unclear and the results of serology and histopathology suggested cystic echinococcosis, the infection caused by *E. granulosus*. Nevertheless, the results of imaging techniques and histopathology often depend on the experience of medical staff and can be associated with some degree to subjective error. Moreover, antigen B used for detection of antibodies to *E. granulosus* shows cross reactivity with *E. multilocularis* (Eckert & Deplazes, 2004; Fecková *et al.*, 2020). Therefore, based also on previous experience of medical personnel and the current epidemiological situation in Slovakia, the molecular analysis of biopsy material was recommended. Afterwards,

the diagnosis of alveolar echinococcosis was confirmed. An early differentiation between alveolar and cystic echinococcosis (before the surgery) plays a key role in the management of the disease, therapy and further prognosis of the patient. The therapeutic approaches are different. On the subject of cystic echinococcosis radical surgery or percutaneous treatment (e.g. PAIR – puncture, aspiration, injection, re-aspiration) with the temporal administration of benzimidazoles is generally indicated. In case of alveolar echinococcosis, the benzimidazole treatment is mandatory in all patients where accepted length of the treatment is 2 years after the complete resection of lesions or for lifetime in all other cases. Radical surgery is the first choice of treatment in all cases suitable for total resection, and interventional procedures are preferred before palliative approach (Brunetti *et al.*, 2010).

In presented case, a secondary metastatic process in the right adrenal gland was detected during the surgery. The metastases can be formed by continuitatem or by haematogenous or lymphatic route (Kern 2010). In the case of adrenal glands, the continuous spread is the most probable. Nevertheless, the primary or secondary involvement of adrenal glands is not frequent. Spahn *et al.* (2016) found information only on eight patients with the primary alveolar echinococcosis of adrenal glands when searched the literature sources published by 2016. Secondary metastases were recorded only in one (herein presented) of 80 Slovak patients recorded at the Institute of Parasitology SAS (Antolová, unpublished data). In France, the extent of AE was assessed in 362 patients, but none of 79 cases with regional extension or metastases suffered from adrenal gland involvement (Piarroux *et al.*, 2011). In Poland, in 30 of 121 AE cases diagnosed between 1990 and 2011 the spread to the other organs was detected, but none was found in adrenal gland (Nahorski *et al.*, 2013). Wang *et al.* (2015) analyzed data of about 159 patients that underwent surgery in Xinjiang, China between 2003 and 2013, and the metastasis in adrenal gland was found in one case. On the other hand, in the study of Kern *et al.* (2003) the most frequently secondary affected organ was the diaphragm (59 of 178 patients with metastases), followed by kidneys and/or adrenal glands (26 of 178 patients).

Alveolar echinococcosis is regarded as a rare and neglected disease, with very few patients referred to the clinicians or hospitals that sometimes have almost none experience with diagnosis and treatment of the disease. Therefore, the conception of networks or establishment of clinical centre (Reference centre) specialized on management of the disease present suitable way to provide the patients with the best care and improve their disease prognosis.

In conclusion, unusual course or clinical picture of the disease together with the lack of medical staff experience can be limiting factors for differential diagnosis of alveolar echinococcosis in the practice. In presented case, results of imaging examinations together with the presence of metastatic lesion in right adrenal gland suggested malignant process. Later, due to uncertain results in histopathology and serology, cystic echinococcosis was thought out, and finally only molecular examination of biopsy material clar-

ified the etiology of the infection. Therefore, we point out on the importance of accurate differential diagnosis of echinococcosis, particularly in the countries with simultaneous occurrence of several *Echinococcus* species. Every aspect of clinical and laboratory results should be considered carefully and responsibly and the use of highly specific molecular techniques is recommended in uncertain cases.

Conflict of Interest

Authors state no conflict of interest.

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References

- ANTOLOVÁ, D., MITERPAKOVÁ, M., ROSOLANKA, R., JAROŠOVÁ, J., FECKOVÁ, M., ONDRISKA, F. (2020): Alveolárna echinokokóza na Slovensku [Alveolar echinococcosis in Slovakia]. *NewsLab*, 11(2): 101 – 102 (In Slovak)
- BRUNETTI, E., KERN, P., VUITTON, D.A., WRITING PANEL FOR THE WHO-IGWE. (2010): Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. *Acta Trop.*, 114: 1 – 16. <https://doi.org/10.1016/j.actatropica.2009.11.001>
- COMBES, B., COMTE, S., RATON, V., RAOUL, F., BOUÉ, F., UMHANG, G., FAVIER, S., DUNOYER, C., WORONOFF, N., GIRAUDOUX, P. (2012): Westward Spread of *Echinococcus multilocularis* in Foxes, France, 2005–2010. *Emerg. Infect. Dis.*, 18(12): 2059 – 2062. <https://dx.doi.org/10.3201/eid1812.120219>
- ECKHERT, J., DEPLAZES, P. (2004): Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. *Clin. Microbiol. Rev.*, 17(1): 107 – 135. DOI: 10.1128/cmr.17.1.107-135.2004
- FECKOVÁ, M., ANTOLOVÁ, D., REITEROVÁ, K. (2020): A comparative study of different immunoassays to detect specific antibodies to *Echinococcus* spp. in human sera. *Helminthologia*, 57(3): 219 – 225. DOI: 10.2478/helm-2020-0025
- GOTTSTEIN, B., WANG, J., BOUBAKER, G., MARINOVA, I., SPILLOTIS, M., MÜLLER, N., HEMPHILL, A. (2015a): Susceptibility versus resistance in alveolar echinococcosis (larval infection with *Echinococcus multilocularis*). *Vet. Parasitol.*, 213(3-4): 103 – 109. DOI: 10.1016/j.vetpar.2015.07.029.
- GOTTSTEIN, B., STOJKOVIC, M., VUITTON, D.A., MILLON, L., MARCINKUTÉ, A., DEPLAZES, P. (2015b): Threat of alveolar echinococcosis to public health – a challenge for Europe. *Trends Parasitol.*, 31(9): 407 – 412. <https://doi.org/10.1016/j.pt.2015.06.001>
- HEGLIN, D., BONTADINA, F., DEPLAZES, P. (2015): Human–wildlife interactions and zoonotic transmission of *Echinococcus multilocularis*. *Trends Parasitol.*, 31(5): 167 – 173. <https://doi.org/10.1016/j.pt.2014.12.004>
- KERN, P. (2010): Clinical features and treatment of alveolar echinococcosis. *Curr. Opin. Infect. Dis.*, 23(5): 505 – 512. DOI: 10.1097/QCO.0b013e32833d7516
- KERN P., BARDONNET K., RENNER E., AUER H., PAWLOWSKI Z., AMMANN RW., VUITTON DA., KERN P., THE EUROPEAN ECHINOCOCCOSIS REGISTRY. (2003): European Echinococcosis Registry: Human alveolar echinococcosis, Europe, 1982–2000. *Emerg. Infect. Dis.*, 9(3): 343 – 349. DOI: 10.3201/eid0903.020341
- KERN, P., WEN, H., SATO, N., VUITTON, D.A., GRUENER, B., SHAO, Y., DELABROUSSE, E., KRATZER, W., BRESSON-HADNI, S. (2006): WHO classification of alveolar echinococcosis: Principles and application. *Parasitol. Int.*, 55: S283 – S287. DOI: 10.1016/j.parint.2005.11.041
- PIARROUX, M., PIARROUX, R., GIORGI, R., KNAPP, J., BARDONNET, K., SUDRE, B., WATELET, J., DUMORTIER, J., GÉRARD, A., BEYTOUT, J., ABERGEL, A., MANTION, G., VUITTON, D.A., BRESSON-HADNI, S. (2011): Clinical features and evolution of alveolar echinococcosis in France from 1982 to 2007: results of a survey in 387 patients. *J. Hepatol.*, 55(5): 1025 – 1033. DOI: 10.1016/j.jhep.2011.02.018
- LICCIOLI, S., GIRAUDOUX, P., DEPLAZES, P., MASSOLO, A. (2015): Wilderness in the ‘city’ revisited: different urban shape transmission of *Echinococcus multilocularis* by altering predator and prey communities. *Trends Parasitol.* 31(7): 297 – 305. <https://doi.org/10.1016/j.pt.2015.04.007>
- MARCINKUTÉ, A., ŠARKUNAS, M., MOKS, E., SAARMA, U., JOKELAINEN, P., BAGRADE, G., LAIVACUMA, S., STRUPAS, K., SOKOLOVAS, V., DEPLAZES, P. (2015): *Echinococcus* infections in the Baltic region. *Vet. Parasitol.*, 213(3-4): 121 – 131. DOI: 10.1016/j.vetpar.2015.07.032
- NAHORSKI, W.L., KNAP, J.P., PAWŁOWSKI, Z.S., KRAWCZYK, M., POLAŃSKI, J., STEFANIAK, J., PATKOWSKI, W., SZOSTAKOWSKA, B., PIETKIEWICZ, H., GRZESZCZUK, A., FELCZAK-KORZYBSKA, I., GOŁĄB, E., WNUKOWSKA, M., PAUL, M., KACPRZAK, E., SOKOLEWICZ-BOBROWSKA, E., NISCIORSKA-OLSEN, J., CZYRZNIKOWSKA, A., CHOMICZ, L., CIELECKA, D., MYJAK, P. (2013): Human alveolar echinococcosis in Poland: 1990–2011. *PLoS Negl. Trop. Dis.*, 7(1): e1986. DOI: 10.1371/journal.pntd.0001986
- PIARROUX M, PIARROUX R, GIORGI R, KNAPP J, BARDONNET K, SUDRE B, WATELET J, DUMORTIER J, GÉRARD A, BEYTOUT J, ABERGEL A, MANTION G, VUITTON DA, BRESSON-HADNI S. (2011): Clinical features and evolution of alveolar echinococcosis in France from 1982 to 2007: Results of a survey in 387 patients. *J. Hepatol.*, 55(5): 1025 – 1033. <https://doi.org/10.1016/j.jhep.2011.02.018>
- REITEROVÁ, K., AUER, H., ALTINTAS, N., YOLASIGMAZ, K. (2014): Evaluation of purified antigen fraction in the immunodiagnosis of cystic echinococcosis. *Parasitol. Res.*, 113: 2861 – 2867. DOI: 10.1007/s00436-014-3947-0
- REUTER, S., NÜSSLE, K., KOLOKYTHAS, O., HAUG, U., RIEBER, A., KERN, P., KRATZER, W. (2001): Alveolar liver echinococcosis: a comparative study of three imaging techniques. *Infection*, 29(3): 119 – 125. DOI: 10.1007/s15010-001-1081-2
- ROMIG, T., DEPLAZES, P., JENKINS, D., GIRAUDOUX, P., MASSOLO, A.,

- CRAIG, P.S., WASSERMANN, M., TAKAHASHI, K., DE LA RUE, M. (2017): Ecology and life cycle patterns of *Echinococcus* species. *Adv. Parasitol.*, 95, 213 – 314. DOI: 10.1016/bs.apar.2016.11.002
- SCHNEIDER, R., GOLLACKNER, B., EDEL, B., SCHMID, K., WRBA, F., TUCEK, G., WALOCHNIK, J., AUER, H. (2008): Development of a new PCR protocol for the detection of species and genotypes (strains) of *Echinococcus* in formalin-fixed, paraffin-embedded tissues. *Int. J. Parasitol.*, 38(8-9): 1065 – 1071. DOI: 10.1016/j.ijpara.2007.11.008
- SPAHN, S., HELMCHEN, B., ZINGG, U. (2016): Alveolar echinococcosis of the right adrenal gland: a case report and review of the literature. *J. Med. Case Rep.*, 10: 325. DOI: 10.1186/s13256-016-1115-0
- VUITTON, D.A., BRESSON-HADNI, S. (2014): Alveolar echinococcosis: evaluation of therapeutic strategies. *Expert Opin. Orphan Drugs*, 2(1): 67 – 86. DOI: 10.1517/21678707.2014.870033
- WAHLSTRÖM, H., LINDBERG, A., LINDH, J., WALLENSTEN, A., LINDQVIST, R., PLYM-FORSHELL, L., OSTERMAN LIND, E., ÅGREN E.O., WIDGREN, S., CARLSSON, U., CHRISTENSSON, D., CEDERSMYG, M., LINDSTRÖM, E., OLSSON, G.E., HÖRNFELDT, B., BARRAGAN, A., DAVELID, C., HJERTQVIST, M., ELVANDER, M. (2012): Investigations and actions taken during 2011 due to the first finding of *Echinococcus multilocularis* in Sweden. *Euro Surveill.*, 12; 17(28):20215. DOI: 10.2807/ese.17.28.20215-en
- WANG, H., LU, C., LIU, X., ZHANG, W. (2015): Metastatic and prognostic factors in patients with alveolar echinococcosis. *Int. J. Clin. Exp. Pathol.*, 8(9): 11192 – 11198