

Specificity Of Diagnosis And Surgical Intervention In Combined Liver Damage Caused By Echinococcosis And Aspergillosis

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Abstract

Aspergillosis is a concept that encompasses a wide range of diseases caused by of the genus Aspergillus fungi. Aspergillus saprophytic mold is widespread in the environment, its spores are easily inhaled. However, despite the fact that most people inhale aspergillus spores daily, aspergillosis develops mainly in immunocompromised individuals (due to illness or during immunosuppressive therapy).

Most often, the lungs are affected, which are the usual portal for the penetration of the fungus, as well as the naso-orbital sinus. There are not so many reports of extrapulmonary aspergillosis. Even rarer in the literature are publications about the coexistence of a saprophytic fungus and a hydatid cyst. Only single clinical observations of the coexistence of aspergillosis and echinococcosis in the lungs have been described. The coexistence of these two pathogens in the liver in the available literature we have not seen.

A clinical observation of a 54-year-old woman with two echinococcal cysts in the liver, in the structure of which Aspergillus was revealed is presented.

The coexistence of liver echinococcosis and aspergillosis is extremely rare. Preoperative verification of the presence of local aspergillosis in this case is practically impossible. However, early diagnosis and treatment in this case are vital, preventing possible complications from becoming infected with these two pathogens. Treatment is based on an early morphological diagnosis and the detection of both pathogens.

Keywords: liver echinococcosis, liver aspergillosis, coexistence of pathogens, diagnosis, treatment, verification.

Objective: to identify the features of tactics in case of combined liver damage with echinococcosis and aspergillosis.

MATERIALS AND METHODS

The results of surgical treatment with the coexistence of echinococcosis and liver aspergillosis were analyzed.

Introduction. Aspergillosis is a concept that covers a wide range of diseases caused by mold fungi of the genus Aspergillus, of which about 200 species have been identified, but a very small number of them cause disease in

humans [1]. The most common pathogenic species is *Aspergillus fumigatus* (*A. fumigatus*) and accounts for more than 90% of all infections. [2].

The mold saprophytic fungus *Aspergillus* is widespread in the environment, its spores are easily inhaled. However, while most people inhale *Aspergillus* spores daily, aspergillosis develops predominantly in immunocompromised individuals (due to disease or immunosuppressive therapy), being the leading cause of death in acute leukemia and hematopoietic cell transplantation. [3].

Invasive *Aspergillus* is a well-recognized cause of invasive fungal disease in an immunosuppressed host. Traditional risk factors identified in advanced aspergillosis are hematologic malignancies, organ transplantation, persistent neutropenia and immunosuppressive conditions secondary to chronic granulomatous disease, human immunodeficiency virus (AIDS) and long-term use of corticosteroids [4], also in patients with chronic obstructive pulmonary disease, liver cirrhosis, transfusion hemosiderosis and diabetes mellitus [5-7]. Recognition of *Aspergillus* infection in critically ill patients and in patients with liver disease has increased in recent years. There are rare cases of invasive aspergillosis in immunocompetent hosts. [4].

Aspergillus infection can be systemic or local, depending on the severity of the body's immune defenses. The most commonly affected are the lungs, which are the usual portal of entry for the fungus, as well as the naso-orbital sinus. The most common forms are allergic bronchopulmonary aspergillosis, aspergilloma (non-invasive aspergillosis) and invasive pulmonary aspergillosis [8]. However, this infection can also affect other organs. Further, according to the frequency of occurrence, the gastrointestinal tract is affected. In disseminated aspergillosis of the gastrointestinal tract, mainly the small or large intestine is affected, less often the upper gastrointestinal tract [9-11], the cardiovascular and central nervous systems [12], detect skin lesions [13, 14].

There are not many published reports of extrapulmonary aspergillosis. One of the major studies is the publication by A. Hori et al., who reviewed 107 autopsy records of patients with invasive aspergillosis. Extrapulmonary aspergillosis was present in 55 patients. Organs involved included heart, kidney, central nervous system, gastrointestinal tract, spleen, liver, thyroid, and pancreas [15].

Other published series are much smaller in number of observations. Yes, S.K. Yeom et al. identified 6 cases of abdominal aspergillosis in immunocompromised patients (4 patients receiving immunosuppressive therapy for solid organ transplantation and 2 patients receiving chemotherapy for acute myeloblastic leukemia). In their study, aspergillosis affected: blood vessels ($n = 3$), liver ($n = 2$), spleen ($n = 2$), gastrointestinal tract ($n = 2$), native kidney ($n = 1$), transplanted kidney ($n = 1$), peritoneum ($n = 1$), and retroperitoneum ($n = 1$) [16]. Single observations of extremely rare localizations are also described, such as, for example, a case of invasive aspergillosis arising from ureteral aspergilloma. [17].

Separately, it is worth mentioning aspergillosis in liver recipients, as a complication of transplantation due to a weakened immune system. Mortality for liver transplant recipients with aspergillosis varies according to various data from 33 to 100% [18-20].

More often after liver transplantation, lung damage is detected [21, 22]. A. Duchini et al. retrospectively reviewed all fungal cultures from 200 liver transplant patients between the years of 1996 and 1999 at one expert information center. Aspergillosis was diagnosed in 6 patients: 5 patients had pulmonary lesions; abscess in the groin - 1. The time from transplantation to infection ranged from 1 week to 34 months [23]. Renal aspergillosis is a rare complication in liver transplant recipients [24, 25]. Aspergillosis of the biliary tract and spine has also been described as single observations in such patients [26, 27]. The literature also presents an extremely rare case of a rare location of aspergillosis in the stomach in a patient who underwent orthotopic liver transplantation [28].

M. Falcone et al., having made and analyzed a review of the English-language literature, found that aspergillosis is a frequent undiagnosed complication in patients with acute liver failure or end-stage liver disease with a mortality rate exceeding 70% [29]. So, L. Fernandez de Orueta et al. described the observation of spinal aspergillosis in a patient with liver cirrhosis [30].

Isolated liver aspergillosis is also detected [31], both by itself and with spread to neighboring organs [32].

Clinical symptoms, including fatigue, weight loss, and low-grade fever, may be present in aspergillosis for weeks or even months before diagnosis, and often mimic manifestations of malignancy or infection [13, 14]. More specific symptoms are due to the localization of the pathological process.

Single-chamber echinococcosis (hydatid echinococcosis) is a severe chronic parasitic disease, helminthiasis caused by the larval stage of tapeworm *Echinococcus granulosus*, characterized by the development of parasitic cysts in

the liver, less often in the lungs, as well as in other organs and tissues [1, 33-38]. The clinical picture and diagnosis of echinococcosis are described in a large number of studies and guidelines and, given the widespread prevalence of this disease, compared with aspergillosis, does not cause difficulties.

Hydatid cyst is a zoonotic disease with an endemic regional distribution, and aspergillus is a saprophytic fungus that can cause allergic aspergillosis, aspergilloma, and semi-invasive and invasive aspergillosis. The coexistence of a saprophytic fungus and a hydatid cyst is extremely rare. N.E. Kocer et al. retrospectively examined 100 cases diagnosed with echinococcal cyst in archival materials to assess the coexistence of aspergillosis and echinococcosis, and only in two patients in the lungs revealed such a combination [39]. The literature describes only a few own clinical observations of the coexistence of aspergillosis and echinococcosis in the lungs. However, these are all observations of a hydatid cyst that has been colonized by *Aspergillus* hyphae in the lungs [1, 33-38]. We did not meet the coexistence of aspergillosis and echinococcosis in the liver in the available literature.

In this regard, we consider it appropriate to present our own clinical observation of the coexistence of echinococcosis and liver aspergillosis.

Clinical observation.

The patient I., 54 years old, was hospitalized in the 3rd surgical department of the Andijan State Medical Institute clinic in May 2018 (case history No. 848/352) with complaints of feelings of heaviness and burning, as well as mild pain in the right hypochondrium, general weakness, malaise, headache, loss of appetite, fever up to 38°C.

Disease history. Since January 2018, the patient began to notice a feeling of heaviness and burning, as well as mild pain in the right hypochondrium. The sensations described above were accompanied by malaise, weakness, headache, fever up to 38°C.

Objectively. General condition upon admission of moderate severity. The patient is undernourished, skin and mucous membranes are of normal color. No pathological changes were found in the respiratory system. An increase in blood pressure up to 180/90 mm Hg was noted. Pulse - 92 beats per minute. The abdomen is moderately enlarged in volume, participates in the act of breathing. On palpation, the abdomen is soft, painful in the right and left hypochondrium, in the epigastric and suprapubic region. An increase in the size of the liver was revealed. Tendency to constipation, urination is normal.

The diagnostic program included generally accepted laboratory and instrumental research methods, ultrasound of the abdominal organs.

The following changes were revealed in the general blood test: hemoglobin - 88 g/l; erythrocytes - $3.56 \times 10^{12}/l$; leukocytes - $8.8 \times 10^9/l$; neutrophils: n / i - 10%, s / i - 70%; lymphocytes - 16%; eosinophils - 1%, an increase in the erythrocyte sedimentation rate (ESR) up to 15 mm/hour.

In the biochemical analysis of blood, an increase in all fractions of bilirubin was revealed: total - 42.59 mmol / l; direct - 33.48 mmol / l; indirect - 9.11 mmol / l.

In the general analysis of urine, a slight increase in leukocytes (10-8-10 in the field of view) was noted.

HBsAg (hepatitis B) - 0.032 - negative, Anti-HCV (hepatitis C) - 0.020 - negative.

ECG: sinus rhythm is correct. Horizontal position of the electrical axis of the heart. Hypoxia in the myocardium. On chest x-ray, the lung pattern is enhanced, the roots are expanded. Expansion of the left ventricle of the heart, bending of the aorta. Diagnosis: chronic bronchitis.

Ultrasound of the abdominal cavity: the liver is enlarged by 1.5 cm, the echogenicity is normal (comparable to the parenchyma of the kidney), the echostructure is fine-grained. In the left lobe of the liver in the projection of II-III segments, a formation is determined, 102 x 91 x 110 mm in size, with clear contours, heterogeneous echostructure, with heterogeneous thick liquid contents and small multi-chamber inclusions inside, a capsule of the formation with a thickness of up to 3-4 mm lies (Fig. 1a), a moderately pronounced acoustic shadow can be traced from the rear wall of the formation. In the projection of segments VII-VIII of the liver, under the diaphragm, a formation similar in structure is detected, with heterogeneous dense liquid content, 56x52 mm in size, with a wall 2-3 mm thick (Fig. 1b).



Figure 1. Ultrasound image of heterogeneous cystic-solid formations of the liver in B-mode: a - in segments II - III of the liver; b - in segments VII-VIII of the liver.

The gall bladder is not changed. Intrahepatic bile ducts are not dilated.

Pathological changes in the pancreas were not revealed.

The spleen is moderately enlarged (area 51 cm²).

Conclusion: Echinococcosis of the left and right lobe of the liver. Moderate enlargement of the spleen.

At the time of admission, the patient had severe pain in the right hypochondrium, radiating to the right shoulder blade, not relieved by analgesics.

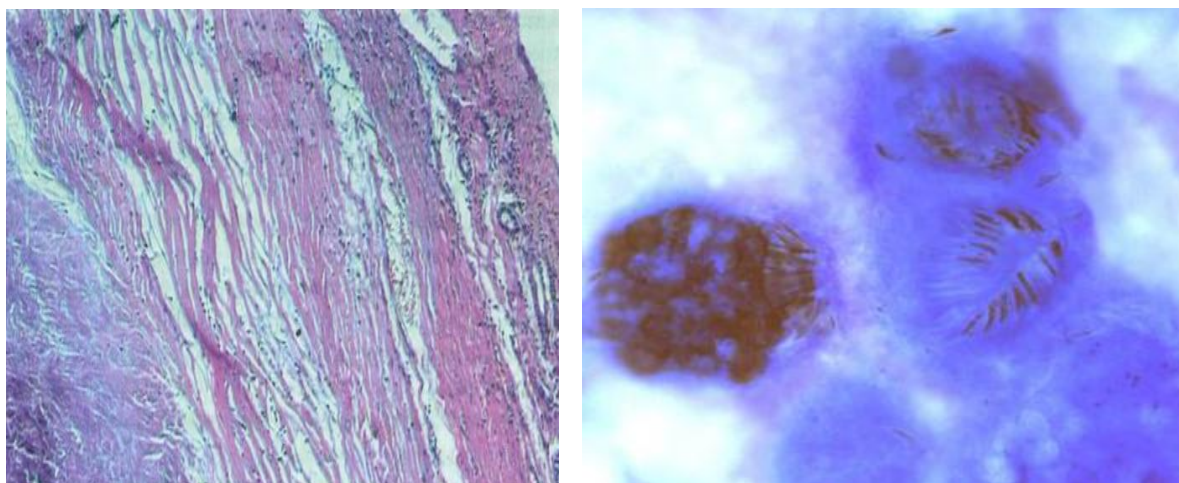
Significant size of the formation and intractable pain caused the implementation of surgical intervention in the following volume: ideal - echinococectomy of the left lobe of the liver (II - III segment pericystectomy). Ideal removal of the cyst of the right lobe of the liver (VIII segment pericystectomy) with drainage of the operation area and subhepatic space.

During the revision in the projection of II-III segments of the left lobe of the liver, a cystic formation was found in a thick capsule with calcifications, 6x5 cm in size, in the projection of the VIII segment of the right lobe, a similar formation was revealed, 7x6 cm in size.

After limiting the cyst of the II-III segments of the liver with gauze napkins moistened with 20% sodium chloride, the cyst was punctured, thick pus was released. The fibrous capsule of the cyst was opened, the chitinous membrane, dead child blisters and necrotic tissues were removed. Produced hemostasis. The residual cavity was treated with 20% formalin, furacillin heated to 700, 96 ° - alcohol, 5% iodine solution, and the inner surface and edge of the capsule were coagulated with an electrocautery. The capsule is maximally removed to healthy tissues.

Next, the round ligament of the liver was mobilized, and the falciform ligament was dissected for manipulations with the cyst of the VIII segment. Produced hemostasis. After limiting the cyst with gauze pads moistened with 20% sodium chloride, the cyst was punctured, thick pus was released. The cyst capsule was opened, mushy purulent content and necrotic tissues were removed. Hemostasis. The residual cavity was treated with 20% formalin, furacillin heated to 700, 96 ° - alcohol, 5% iodine solution, and the inner surface and edge of the capsule were coagulated with an electrocautery. The capsule is maximally removed to healthy tissues. With repeated revision of the liver and abdominal organs, no pathological changes were found. Sanitation of the abdominal cavity with furacillin was performed.

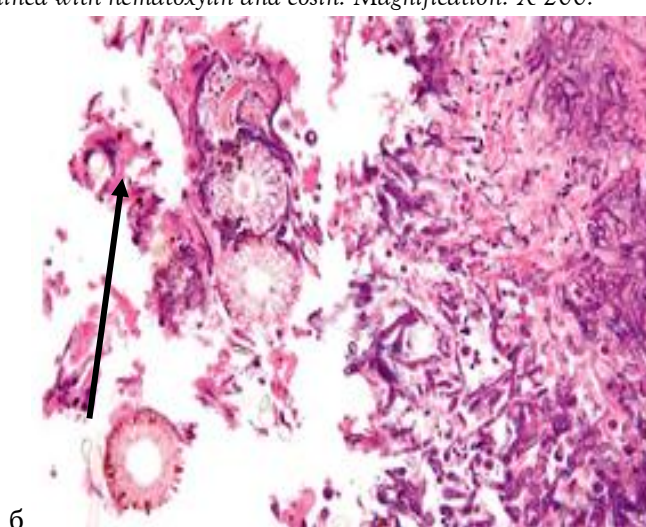
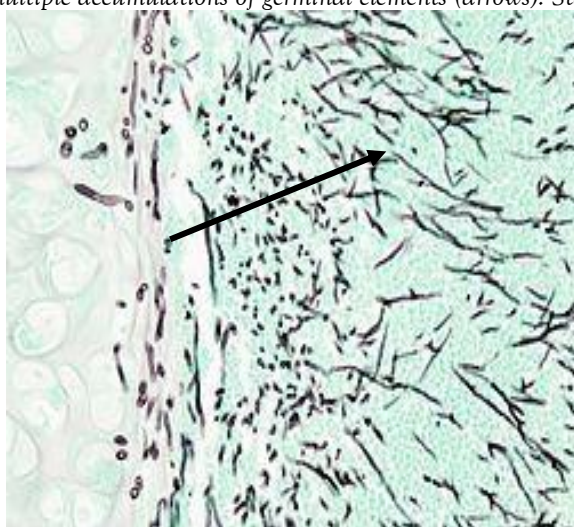
The removed chitinous membrane, daughter cysts and purulent content of the formation of the II segment of the liver and the mushy liquid content of the formation of the VIII segment of the liver were sent for histological examination.



a

b

Figure 2. Histological preparations of liver echinococcosis: *a* - fibrous capsule (1 - inner layer of necrosis, 2 - hyaline layer, 3 - loose fibrous connective tissue). Stained with hematoxylin and eosin. Magnification: X 56. *b*) germinal membrane with multiple accumulations of germinal elements (arrows). Stained with hematoxylin and eosin. Magnification: X 200.



a

b

Figure 3. Histological preparations of liver aspergillosis: *a* - mycelial filaments (arrow) and fruiting organs are detected. Stained with hematoxylin and eosin. Magnification: X 400; *b* - conidiophores of conidia (arrow). Stained with hematoxylin and eosin. Magnification: X 100.

RESULTS. Histological examination. The material was fixed in 10% neutral formalin solution. Paraffin sections 3-4 microns thick, made on a Leica SM 2000R sledge microtome, stained with hematoxylin and eosin. The histological picture of the 1st preparation is represented by a connective tissue capsule with polymorphocellular inflammation, eosinophilia, limiting the focus of echinococcosis; germinal membrane with multiple accumulations of germinal elements (Figure 2).

The histological picture of the 2nd preparation appears to be necrotic tissues with massive inflammatory infiltrates, consisting of lymphocytes, plasma cells, numerous nuclei of giant cells of a random nature are also noted, with the growth of fungal filaments. The largest number of inflammatory cells was found along the periphery of the accumulations of hyphae of the fungus in the form of a belt, mainly represented by eosinophils with individual lymphocytes, plasmocytes, macrophages and neutrophils (Figure 3).

Conclusion: Echinococcosis and aspergillosis of the liver.

To confirm the parasitic pathology, *immunological diagnostics* was carried out in the laboratory of the Central Scientific Research Laboratory of the State Medical Institute:

CONCLUSION: The reaction of indirect hemagglutination, enzyme immunoassay, based on the detection of antibodies (IgG and IgE) in the blood serum of the invaded, which are specific markers of fungal infection.

In the postoperative period, antiparasitic chemotherapy for echinococcosis was immediately started (Albendazole 400 mg 2 times a day, Furazolidone 0.05 mg 1 tablet x 3 times a day, Metronidazole 250 mg x 2 times a day) in combination with hepatoprotective therapy (Heptral 10 ml in 0.9% sodium chloride solution intravenously) and immunological correction (Timolin 1.0 intramuscularly).

Later, after identifying a concomitant infection of aspergillosis, the patient was additionally given antifungal therapy (Teknazol 100 mg orally, Amphotericin 50,000 mcg (IU) intravenously).

The patient was re-interviewed to determine the cause of a possible invasion and / or reduced immunity.

The patient lives in a rural area, a housewife, mainly engaged in housework and caring for livestock.

Since the localized form of aspergillosis is rare, and dissemination of the process can be found in almost most organs, the whole body MSCT was performed in the postoperative period to exclude a disseminated lesion. The study confirmed local liver damage.

In the postoperative period, minor fluid accumulations were detected in the surgical intervention area, which independently regressed.

The program of intensive antiparasitic, antifungal and hepatoprotective therapy in combination with detoxification and immunological therapy allowed, compared with the initial values, to reduce the level of bilirubinemia in the patient due to both of its fractions, to reduce the severity of endogenous intoxication.

The patient was discharged on the 7th day after the operation.

When examined in dynamics after 3, 6 months and a year later, the patient has no complaints, no recurrence of the disease was detected according to the radiation methods of the study.

DISCUSSION. Aspergillosis has traditionally been regarded as an infection occurring mainly in patients with well-established risk factors such as neutropenia, hematologic malignancies, organ transplantation, or HIV [5]. In the early 2000s, researchers began to emphasize the increasing role in the development of aspergillosis of such factors as long-term use of low doses of corticosteroids, the presence of chronic obstructive pulmonary disease, liver cirrhosis, hemosiderosis, blood transfusion, and diabetes mellitus [5-7]. There is growing evidence that apparently immunocompetent patients, such as those with severe liver disease, are also at high risk of aspergillosis infection. M. Falcone et al. in 2011 searched the MEDLINE database for English-language reports of invasive aspergillosis in patients with liver disease published from 1973 to November 2009 (74 sources) Key words were: aspergillus infections, invasive aspergillosis, end-stage liver disease, cirrhosis of the liver, liver failure, acute hepatitis. For the purposes of this study, cases occurring in liver transplant recipients, hematological patients, or patients with HIV were excluded. The authors confirmed that aspergillosis is a common undiagnosed complication in patients with acute liver failure or end-stage liver disease, with a mortality rate exceeding 70% [29]. Previously, patients with acute or progressive liver disease were considered to be at some risk of aspergillosis only as a result of immunosuppression after liver transplantation. However, liver disease alone predisposes to bacterial and fungal infections by reducing both humoral and cellular immunity [40].

Despite the presence of all these predisposing factors, patients with acute or advanced liver disease are not usually considered by physicians as a population at risk for developing aspergillosis, making the diagnosis difficult. This

is confirmed in the analysis by M. Falcone et al., where the majority of cases of aspergillosis (52.8%) were diagnosed postmortem [29]. These data reflect clinicians' lack of awareness of the risk of aspergillosis in non-neutropenic patients and, as a result, the difficulty of making a clinical diagnosis.

In the presence of liver echinococcosis, the level of bilirubin in the blood is higher than the standards. According to Maslennikova N.A. et al. its maximum concentration was noted in patients with a disease duration of 5-8 years, and the activity of liver enzymes significantly ($p < 0.05$) exceeds the upper limit of the standard in groups with a duration of infection of 5-8 years and 9 years or more (by 25-80, 0% for AST and ALT, respectively) [41]. The results obtained indicate that with a long course of the disease in patients with liver echinococcosis, the metabolic and synthetic function of hepatocytes changes, which can also be a predisposing factor to the development of aspergillosis.

In the presented clinical observation, echinococcal cysts are of medium size. According to the ultrasound study, the contents of the cysts are heterogeneous (against the background of the presence of elements of daughter cysts, there is a pronounced heterogeneity of the liquid content, a thickening of the capsule). There is also an increase in temperature to 38 °C and changes in some parameters of the general and biochemical blood tests, as well as indicators of endogenous intoxication. All of the above could make it possible to suspect suppuration of an echinococcal cyst. However, it did not allow us to talk about the development of aspergillosis in echinococcal cysts, either from the point of view of pathognomonic manifestations, or from the point of view of the frequency of occurrence. At the same time, the suppuration of both cysts, determined during the surgical intervention, prompted a more extended morphological study of the removed material. As a result, a combination of echinococcosis and liver aspergillosis was revealed. The data obtained made it possible to correct postoperative therapy (antifungal therapy was additionally carried out), which, in general, in combination with antiparasitic, hepatoprotective, detoxification and immunological therapy, made it possible to correct the general condition and, in the future, to exclude the recurrence of the disease.

Conclusion. The coexistence of aspergillosis and liver echinococcosis is extremely rare. Preoperative verification of the presence of local aspergillosis in this case is practically impossible. However, early diagnosis and treatment in this case is vital, preventing possible complications from infection with these two pathogens. Treatment is based on early morphological diagnosis and identification of both pathogens. Only pathomorphological studies of the surgical material gave grounds to diagnose liver aspergillosis, and complex drug treatment in combination with antifungal therapy led to the patient's recovery.

REFERENCES

1. Castillo-Minaya K.Y., Cherre-Fiestas A.C., Somocurcio-Peralta J.R. Coexistencia de Aspergilosis e Hidatidosis Pulmonar. Reporte de un caso [Coexistence of Pulmonary Aspergillosis and Hydatidosis. Case report]. *Rev Peru Med Exp Salud Publica*. 2018 Oct-Dec; 35(4): 689-694. doi: 10.17843/rpmesp.2018.354.3437.
2. Chen S., Pu J.L., Yu J., Zhang J.M. Multiple Aspergillus cerebellar abscesses in a middle-aged female: Case report and literature review. *Int. J. Med. Sci*. 2011; 8: 635-639. doi:10.7150/ijms.8.635
3. Oren I., Goldstein N. Invasive pulmonary aspergillosis. *Curr. Opin. Pulm. Med*. 2002; 8: 195-200. doi: 10.1097/00063198-200205000-00008
4. Varidhi N., Benjamin U., Adjoa Z., Erica H. Invasive Aspergillosis of the Liver in an Immunocompetent Patient. November 2019; 27(6): 370-373. doi: 10.1097/IPC.0000000000000787
5. Segal B.H., Walsh T.J. Current approaches to diagnosis and treatment of invasive aspergillosis. *Am J Respir Crit Care Med*. 2006 Apr 1; 173(7): 707-717. doi: 10.1164/rccm.200505-727SO.
6. Meersseman W., Lagrou K., Maertens J., Van Wijngaerden E. Invasive aspergillosis in the intensive care unit. *Clin Infect Dis*. 2007 Jul 15; 45(2): 205-216. doi: 10.1086/518852.
7. Bulpa P., Dive A., Sibille Y. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Eur Respir J*. 2007 Oct; 30(4): 782-800. doi: 10.1183/09031936.00062206.
8. Kousha M., Tadi R., Soubani A.O. Pulmonary aspergillosis: a clinical review. *European Respiratory Review*. 2011; 20: 156-174. doi: 10.1183/09059180.00001011
9. Cha S.A., Kim M.H., Lim T.S., Kim H.H., Chang K.Y., Park H.S., Kim H.W., Wie S.H., Jin D.C. Invasive Primary Colonic Aspergillosis in the Immunocompetent Host without Classical Risk Factors. *Yonsei Med J*. 2015 Sep; 56(5): 1453-6. doi: 10.3349/ymj.2015.56.5.1453.
10. Di Franco G., Tagliaferri E., Pieroni E., Benedetti E., Guadagni S., Palmeri M., Furbetta N., Campani D., Di Candio G., Petrini M., Mosca F., Morelli L. Multiple small bowel perforations due to invasive aspergillosis in a patient with acute myeloid leukemia: case report and a systematic review of the literature. *Infection*. 2018 Jun; 46(3): 317-324. doi: 10.1007/s15010-018-1115-7.
11. Kulkarni A.A., Aruni A., Rastogi P., Rana S., Gupta R. Invasive aspergillosis causing gastric necrosis and perforation: A case report. *JGH Open*. 2019 Feb 27; 4(1): 90-93. doi: 10.1002/jgh3.12157.
12. Boes B., Bashir R., Boes C., Hahn F., McConnell J.R., McComb R.J. Central nervous system aspergillosis. Analysis of 26 patients. *Neuroimaging*. 1994 Jul; 4(3): 123-129. doi: 10.1111/jon199443123.

13. Wightman S.C., Kim A.W., Proia, L.A., Faber L.P., Gattuso P., Warren W.H., Liptay M.J. An unusual case of *Aspergillus* fibrosing mediastinitis. *Ann. Thorac. Surg.* 2009; 88: 1352–1354. doi: 10.1007/s11606-013-2528-8
14. Rossouw I., Goedhals D., van der Merwe J., Stellenberg V., Govender N. A rare, fatal case of invasive spinal aspergillosis in an antiretroviral-naïve, HIV-infected man with pre-existing lung colonization. *J. Med. Microbiol.* 2011; 60: 1534–1538. doi: 10.1099/jmm.0.031146-0
15. Hori A., Kami M., Kishi Y., Machida U., Matsumura T., Kashima T. Clinical significance of extra-pulmonary involvement of invasive aspergillosis: a retrospective autopsy-based study of 107 patients. *J Hosp Infect.* 2002 Mar; 50(3): 175-182. doi: 10.1053/jhin.2001.1170.
16. Yeom S.K., Kim H.J., Byun J.H., Kim A.Y., Lee M.G., Ha H.K. Abdominal aspergillosis: CT findings. *Eur J Radiol.* 2011 Mar; 77(3): 478-482. doi: 10.1016/j.ejrad.2009.08.016.
17. Choi H., Kang I.S., Kim H.S., Lee Y.H., Seo I.Y. Invasive aspergillosis arising from ureteral aspergilloma. *Yonsei Med J.* 2011 Sep; 52(5): 866-868. doi: 10.3349/ymj.2011.52.5.866.
18. Singh N., Avery R.K., Munoz P., Pruett T.L., Alexander B., Jacobs R., Tollemar J.G., Dominguez E.A., Yu C.M., Paterson D.L., Husain S., Kusne S., Linden P. Trends in risk profiles for and mortality associated with invasive aspergillosis among liver transplant recipients. *Clin Infect Dis.* 2003 Jan 1; 36(1): 46-52. doi: 10.1086/345441.
19. Fortún J., Martín-Davila P., Moreno S., Barcena R., de Vicente E., Honrubia A., García M., Nuño J., Candela A., Uriarte M., Pintado V. Prevention of invasive fungal infections in liver transplant recipients: the role of prophylaxis with lipid formulations of amphotericin B in high-risk patients. *J Antimicrob Chemother.* 2003 Nov; 52(5): 813-819. doi: 10.1093/jac/dkg450.
20. Barchiesi F., Mazzocato S., Mazzanti S., Gesuita R., Skrami E., Fiorentini A., Singh N. Invasive aspergillosis in liver transplant recipients: epidemiology, clinical characteristics, treatment, and outcomes in 116 cases. *Liver Transpl.* 2015 Feb; 21(2): 204-212. doi: 10.1002/lt.24032.
21. Lin Q.Y., Zhao Y.H., Yan L.N., Huang A.H., Li B., Lu S.C., Zeng Y., Wen T.F., Zhao J.C., Cheng N.S. Diagnosis and treatment of lung aspergillosis after liver transplantation. *Zhonghua Wai Ke Za Zhi.* 2003 Jan; 41(1): 17-18.
22. Park Y.S., Seo J.B., Lee Y.K., Do K.H., Lee J.S., Song J.W., Song K.S. Radiological and clinical findings of pulmonary aspergillosis following solid organ transplant. *Clin Radiol.* 2008 Jun; 63(6): 673-680. doi: 10.1016/j.crad.2007.12.009.
23. Duchini A., Redfield D.C., McHutchison J.G., Brunson M.E., Pockros P.J. Aspergillosis in liver transplant recipients: successful treatment and improved survival using a multistep approach. *South Med J.* 2002 Aug; 95(8) :897-899. doi: 10.1097/00007611-200208000-00021.
24. Meng X.C., Jiang T., Yi S.H., Xie P.Y., Guo Y.F., Quan L., Zhou J., Zhu K.S., Shan H. Renal aspergillosis after liver transplantation: clinical and imaging manifestations in two cases. *World J Gastroenterol.* 2014 Dec 28; 20(48): 18495-502. doi: 10.3748/wjg.v20.i48.18495.
25. Araos-Baeriswyl E., Moll-Manzur C. Renal aspergillosis after liver transplant: Report of an unusual case. *Gastroenterol Hepatol.* 2018 Jan; 41(1): 30-31. doi: 10.1016/j.gastrohep.2016.11.011.
26. Yuchong C., Dingheng Z., Zhizhong Y., Hongyu Y., Jing H., Jianghan C. Aspergillosis of biliary tract after liver transplantation: a case report. *Mycopathologia.* 2010 Aug; 170(2): 117-121. doi: 10.1007/s11046-010-9300-y.
27. Leung V., Stefanovic A., Sheppard D. Severe cerebral aspergillosis after liver transplant. *Transpl Infect Dis.* 2010 Feb; 12(1): 51-53. doi: 10.1111/j.1399-3062.2009.00461.x.
28. Sulik-Tyszka B., Figiel W., Krawczyk M., Wróblewska M. Invasive Aspergillosis of the Stomach and Co-infection With *Candida krusei* in a Patient With Terminal Liver Failure: A Case Report. *Transplant Proc.* 2016; 48(9): 3149-3152. doi:10.1016/j.transproceed.2016.06.036.
29. Falcone M., Massetti A.P., Russo A., Vullo V., Venditti M. Invasive aspergillosis in patients with liver disease. *Medical Mycology.* May 2011; 49: 406–413. doi:10.3109/13693786.2010.535030
30. Fernandez de Orueta L., Andrés R., Elías T., Pintado V. Aspergilosis vertebral en un paciente cirrótico: una causa infrecuente de espondilitis [Vertebral aspergillosis in a cirrhotic patient: an uncommon cause of spondylitis]. *Enferm Infecc Microbiol Clin.* 2012; 30(4): 219-220. doi:10.1016/j.eimc.2011.11.002.
31. Ito A. Hepatic aspergillosis. *Ryoikibetsu Shokogun Shirizu.* 1999; 24(Pt 2): 323-324.
32. Chen L., Liu Y., Wang W., Liu K. Adrenal and hepatic aspergillosis in an immunocompetent patient. *Infect Dis (Lond).* 2015 Jun; 47(6): 428-432. doi: 10.3109/00365548.2014.995697.
33. Bal A., Bagai M., Mohan H., Dalal U. Aspergilloma in a pulmonary hydatid cyst: a case report. *Mycoses.* 2008 Jul; 51(4): 357-359. doi: 10.1111/j.1439-0507.2008.01495.x.
34. Agarwal S., Bohara S., Thakran A., Arora P., Singh R., Agarwal P.N. Pulmonary hydatid disease with coexistent aspergillosis: an incidental finding. *Indian J Med Microbiol.* 2013 Jan-Mar; 31(1): 85-86. doi: 10.4103/0255-0857.108740.
35. Aliyali M., Badali H., Shokohi T., Moazeni M., Nosrati A., Godazandeh G., Dolatabadi S., Nabili M. Coinfection of Pulmonary Hydatid Cyst and Aspergilloma: Case Report and Systematic Review. *Mycopathologia.* 2016 Apr; 181(3-4): 255-265. doi: 10.1007/s11046-015-9974-2.
36. Aala F., Badali H., Hashemi Fesharaki S., Boroumand M., Sotoudeh Anvari M., Davari H., Agha Kuchak Afshari S., Khodavaisy S. Coexistence of aspergilloma and pulmonary hydatid cyst in an immunocompetent individual. *J Mycol Med.* 2017 Sep; 27(3): 396-399. doi: 10.1016/j.mycmed.2017.04.006.
37. Goyal R.C., Tyagi R., Garg B., Mishra A., Sood N. Pulmonary Hydatid Disease with Aspergillosis - An Unusual Association in an Immunocompetent Host. *Turk Patoloji Derg.* 2019; 35(2): 166-169. doi: 10.5146/tjpath.2017.01396.
38. Aboksari M.S., Safavi M. Concomitant Pulmonary Cystic Echinococcosis and Aspergillosis in a Male Child. *Journal of Tropical Pediatrics, fmaa020*, doi: 10.1093/tropej/fmaa020. Published: 04 May 2020
39. Kocer N.E., Kibar Y., Guldur M.E., Deniz H., Bakir K. A retrospective study on the coexistence of hydatid cyst and aspergillosis. *Int J Infect Dis.* 2008; 12(3): 248–51. doi: 10.1016/j.ijid.2007.08.005

40. Cheruvattath R., Balan V. Infections in Patients With End-stage Liver Disease. *J Clin Gastroenterol*. 2007 Apr; 41(4): 403-411. doi: 10.1097/01.mcg.0000248018.08515.f9.

41. Масленникова Н.А., Тихонова Е.П., Михайлова Л.А. Клинические аспекты проявления эхинококкоза печени. *Современные проблемы науки и образования*. 2018; 5: <http://www.science-education.ru/ru/article/view?id=27998> (дата обращения: 17.06.2020). [Maslennikova N.A., Tikhonova E.P., Mikhailova L.A. Clinical aspects of the manifestation of liver echinococcosis. *Modern problems of science and education*. 2018; 5: <http://www.science-education.ru/ru/article/view?id=27998> (accessed: 06/17/2020). In Rus.]