FUNGI AND GROWTH FACTORS IN LIVER OF MINK INFECTED WITH ALEUTIAN DISEASE

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ABSTRACT. *When mink are infected with Aleutian disease, the immune protection is impaired. In the present work we have studied the prevalence of fungal flora in the liver of 18 dark brown minks infected with Aleutian disease. We isolated 12 genus of moulds. Members of the genus Candida, Aspergillus and Penicillium were the most frequently isolated strains. Our results demonstrated that the distribution of hyphae were between hepatocytes in all areas of liver acinus, but yeastlike cells – mainly in interlobular bile ducts.We studied VEGF and HGF expression by immunohistochemistry. Results suggested the expression of VEGF in blood vessels (around central veins) and mainly in periportal hepatocytes, consequently, this factor is expressed in areas of the liver, which are moderately and/or richly supplied with oxygen. Allocation of HGF in hepatocytes was observed uniform or non uniform, frequently around bile-ducts and portal tracts.In conclusion, detection of VEGF and HGF simultaneously to inflammation liver might be connected to the tissue ischemia and damage realized by the same inflammatory cells.*

Key words: *mink, liver, mycoses, vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF)*

Introduction

Aleutian disease (AD) is a chronic, progressive, non-treatable disease of mink caused by parvovirus. When mink are infected with AD, the immune protection is impaired (Hunter, Lemieux, 1996) and microscopic fungi can disseminate via blood vessels in the body.

Vascular lesions occur most commonly in the gastrointestinal and hepatic arteries (Porter *et al.*, 1973; Hunter, Lemieux, 1996). Vascular endothelial growth factor (VEGF) is one of the strongest regulators of vascular permeability (Esser *et a*l., 1998; Nolan *et al*., 2004). VEGF promotes vascular disruption, increases vascular permeability and contributes inflammation process (Taniguchi *et al*., 2001).

The liver is able to regenerate after damage. Cytokine hepatocyte growth factor (HGF) that is a potent mitogen of hepatocytes, performs multiple activities after liver injury (Watanabe *et al*., 2003; Hironobu *et al*., 2006). HGF molecules are distributed to the liver, spleen, kidney and adrenal glands (Zioncheck, 1994). Sinusoidal endothelial cells and Kupffers cells contain HGF in normal liver (Maher, 1993), but during liver regeneration HGF is mainly produced by hepatic stellate cells (HSC) (Hironobu *et al*., 2006), as well as fibroblasts, epithelial and endothelial cells, hepatocytes and Kupffers cells (Maher, 1993). As a result HGF participates in angiogenesis, morfogenesis and decreases cell apoptosis (Funakoshi, Nakamura, 2003).

The aim of present study were detecting of a possible correlation between dissemination of fungi and expression of growth factors in liver of mink infected with AD.

Materials and Methods

Animals and tissue preparation

To detect the fungal infection and growth factors in the liver, 18 dark brown mink at an age of seven months were selected randomly. The animals were brought from a fur farm of Riga district. All mink were positive to virus of AD used reaction of imunoelectroosmophoresis.

These mink were anaesthetized with 1 ml 1% solution of ditilini (Jepsen *et al*., 1981). Each liver sample was collected in a sterile bag for mycological examination and fixed in 12 % formalin too, embedded in paraffin and used for periodic acid – Schiff (PAS) staining and immunohistochemistry.

Mycological examination

Sabouraud's agar was used as a primary isolation medium for the fungal cultures from the mink liver specimens (Willard *et al*., 1994). A small surface of the changed tissue was burned on a flame, and small pieces of tissue from the middle were cut out with sterile scissors. The tissue cuts were used for a stripe-like inoculation onto media (Spesivceva, 1964) or they were placed on the agar surface (4–5 small tissue pieces in size of 0.5 cm X 0.5 cm (Quinn *et al.,* 1994).

All mycological inoculates on Petri plates were incubated in a thermostat for 4 weeks at a temperature of +26ºC (Quinn *et al*., 1994; Kuznecov, 2001). The microscopic identification of the isolated fungi was carried out according to conventional methods (Sarkisov *et al*., 1953; Kwon-Chung, Bennett, 1992; Bridson, 1993; Larone, 1995; Kirilenko, 1997; Ulloa, Hanlin, 2000; Sutton *et al*., 2001).

PAS method

PAS method is a punctual method for detection of microscopic fungi in tissues. PAS staining painted microscopic fungi as pinkish red elements (Quinn *et al.,* 1994).

Multiple 6 µm-thick sections of the paraffin-embedded mink livers were deparaffinized, rehydrated, processed with 0.5% K_2SO_4 solution, washed in distillate water and seated in Shiff reagent.

Hematoxylin was used for the counterstain. After tissue dehydratation, processing with polystirol was carried out.

Immunohistochemistry

Multiple 6 µm-thick sections of the paraffin-embedded mink livers were examined for immunohistochemistry. The primary antibodies utilized in immunohistochemistry were rabbit polyclonal antibodies specific for VEGF (dilution 1:50; code M7273, DakoCytomation, Denmark) and HGF (dilution 1:300; code AF294NA, R&D System, Germany).

Prior to immunostaining, sections were deparaffinized and rehydrated. Sections were processed in microwave for 20 min in 4% citrate buffer (pH 10), quenched for 10 min with 3% H_2O_2 for blocking endogenous peroxidase activity, rinsed in phosphate-buffered saline (pH 7.4), pretreated with a nonimmune goat serum for 10 min for blocking of nonspecific antibody binding and then incubated for 2 h with the primary antibodies. Immunoreaction was visualized by the other antibodies – avidin-biotin (LSAB) immunoperoxidase method using an LSAB kit (code K1015, DakoCytomation, Denmark) and DAB (diaminobenzidine) solution (code K3468, Dako, Denmark) was used as chromogen, and hematoxylin was used as the counterstain.

Statistical analysis

For quantitative analysis we used a counting of inflammation cells in three fields of vision. Semi-quantitative analysis was used to estimate proportions of immunopositive cells in liver (Pilmane *et a*l., 1998).

Results

Microscopic fungi in the liver

Micological examination showed a broad contamination with microscopic fungi in mink liver (Figure 1) (Arthrographis kalrae, Aspergillus spp., Aureobasidium pullulans, Candida spp., Chaetomium spp., Cladosporium sphaerospermum, Emmonsia spp., Penicillium spp., Scedosporium prolificans, Sporothrix cyanescens, Wangiella spp.).

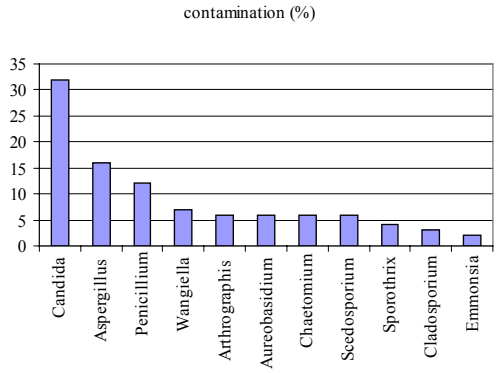

Figure 1. Presence of fungi genus in mink liver

The occurrence of fungi genus was: Candida 32%, Aspergillus 16%, Penicillium 12%, Wangiella 7%, Arthrographis, Aureobasidium, Chaetomium, Scedosporium – each per 6%, but Sporothrix 4%, Cladosporium 3% and Emmonsia 2%.

Our findings in mink liver show distribution of hyphae between hepatocytes in all area of liver acinus, but yeaslike cells – mainly in interlobular bile ducts (Figure 2) and in small numbers between hepatocytes in periportal area closely to triadas and around central veins.

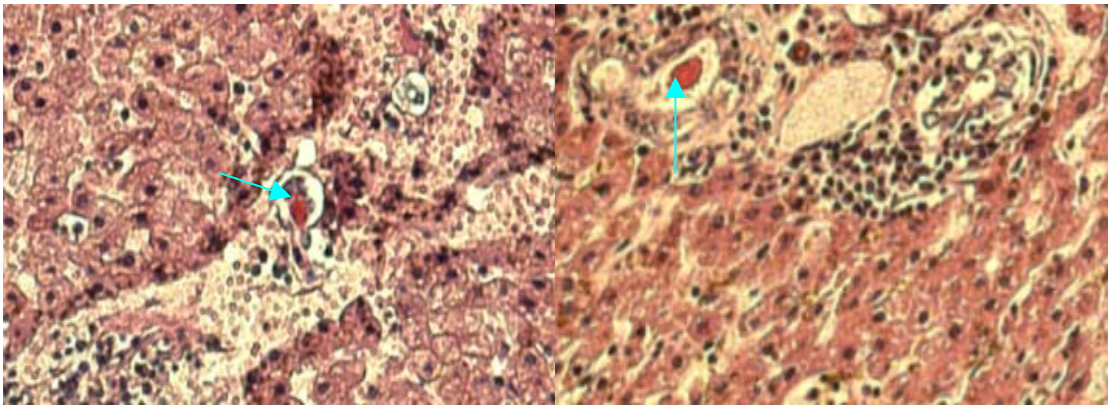

Figure 2. Microscopic fungi in bile ducts of mink liver (arrows, PAS, X 200)

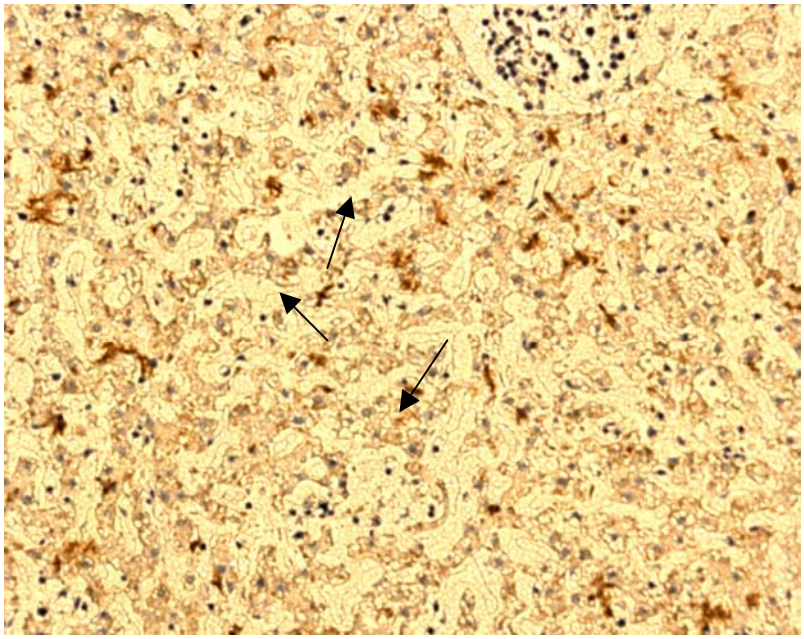

Figure 3. Medium VEGF expression in the mink liver (arrows, biotin-streptavidin IMH, X 200)

Vascular endothelial growth factor (VEGF)

Research results suggested expression of VEGF in blood vessels in deoxygenated area of liver, but also in periportal hepatocytes (Figure 3).

The increasing of VEGF activity in periportal hepatocytis we found in the zones, where yeastlike forms of the microscopic fungi and the Kupffer cells were observed.

The activity of VEGF is inducing disruption of the blood vessels (Esser *et al*., 1998), but our research does not suggest a positive relation between inflammation cells and intensity of VEGF expression (Figure 4), which possibly confirms persistence of the agent with an impact on VEGF.

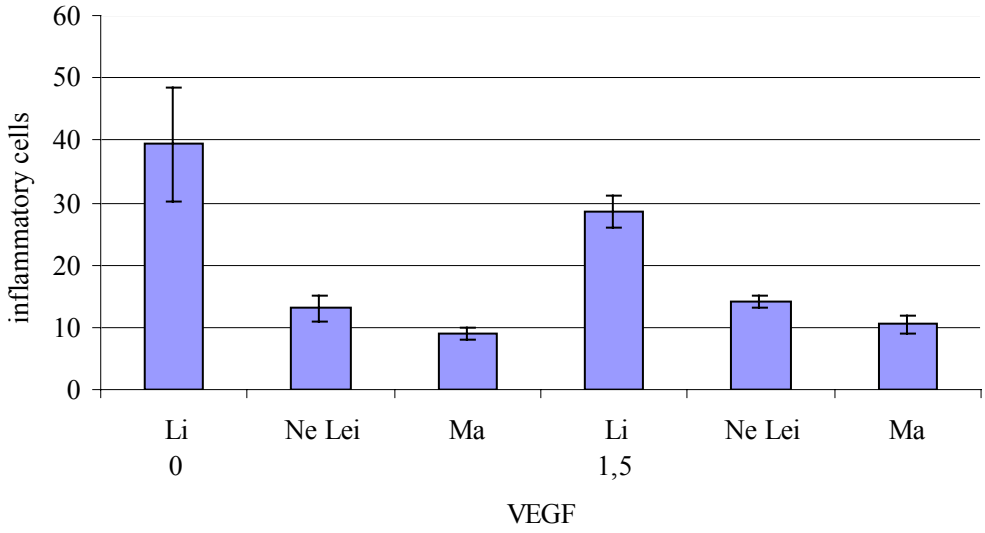

Figure 4. Relation between inflammation cells and VEGF in the mink liver

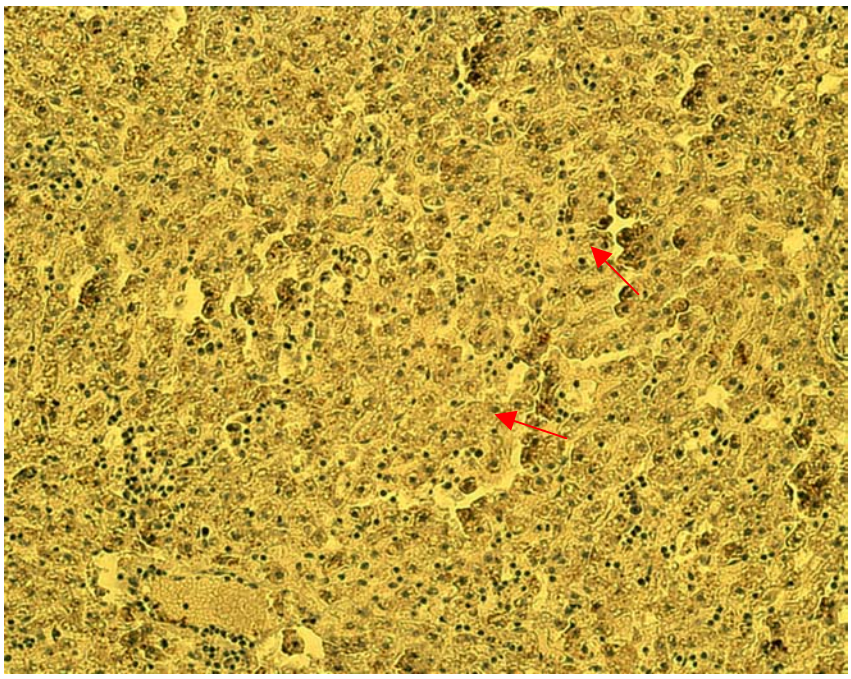

Figure 5. Localization of HGF in the mink liver (arrows, biotin-streptavidin IMH, X 200)

Hepatocyte growth factor (HGF)

HGF expression were found in the liver samples of all mink examined. We mainly observe allocation of HGF in hepatocytes (Figure 5), uniform or non uniform, frequently around bile ducts and portal tracts.

The expression of these growth factor we found in the zones, where lot of the microscopic fungi and the inflammation cells were observed. It is suggesting of possible stimulation activity regarding HGF.

Discussion

Proverbial, that portal vena (v.porta) with support of v.mesenterica superior, v.mesenterica inferior, v.lienalis, v.cystica, v.gastrica sinistra, v.gastrica dextra un v.pregastrica collects blood from the digestive tract, spleen, bile-cyst and pancreas (Jubb *et al*., 1993). Thereby there is a possibility of penetration in liver of peroraly received microscopic fungi in addition to impaired immune protection.

Most frequently Candida spp., Aspergillus spp. and Penicillium spp. were detected. Sutton *et al*. (2001) also confirms that they are mostly disseminated infection agents. Most of the established microscopic fungi are described in literature as widely spread environmental contaminants (Degavre *et al*., 1997; Hubalek *et al*., 1998; Ponton *et al*., 2000).

Contamination of animal liver with Aspergillus spp. is also confirmed by other researchers (Carter, Chengappa, 1993; Quinn *et al*., 1994; Myrvik, Weiser, 1988; Kuznecov, 2001; Carter, Wise, 2004). Althought pathogenic properties of Aspergillus genus are less clear (Müllbacher, Eichner, 1984), nevertheless we suggest, that ability of Aspergillus spp. to cause proteases promotes its distribution in mink liver, because protease could either assist tissue penetration by the fungus or degrade some critical host defense factor (Kwon-Chung, Bennett, 1992).

Our finding of Candida spp. in the liver supports data of other researchers, who report generalization of mycosis (Macsween *et al*., 1979; Braude, 1982; Carter, Chengappa, 1993; Quinn *et al*., 1994; Zanata *et al*., 2006). Substantially, the data suggest that the main place of invasion of deep candidosis is oesophagus and stomach (Eras *et al*., 1972). Possibly, oesophagus and stomach, constitute the entrance for infection with minks.

Our finding of Arthrographis kalrae in experimental mink liver confirms Kwon-Chung and Bennett (1992) studies, who report pathogenity of aforementioned microscopic fungi concerning mice. Possibly, dimorfisms (growth ability at 37°C to 45°C) of Arthrographis kalrae explain our results (Sutton *et al*., 2001).

Similarly Chaetomium spp. show ability to induce allergic reactions (Feier *et al*., 1966) and systemic mycosis (Sutton *et al*., 2001). Our findings confirm the data of the above mentioned reports regarding Chaetomium genus as a possible causative agent of systemic mycosis.

Our finding of Sporothrix cyanescens is confirmed by other scientists, who isolated this yeastlike microscopic fungi from animal viscera (Feier *et al*., 1966; Kuznecov, 2001). Although animal mycosis sporotrihosis mainly is induced by Sporothrix schenckii (Feier *et a*l., 1966; Kuznecov, 2001). At the same time other author (Spesivceva, 1964) reported others species for Sporotrichum, which are able to penetrate into the organism via skin and mucous membrane wounds.

Wangiella spp. microscopic fungi mainly induce subcutaneus mycosis of cats, dogs, horses, goats and other animals (Quinn *et al*., 1994). Our finding of Wan-

giella spp. are confirmed by other authors, who indicate the ability of aforementioned microscopic fungi to generate systemic mycosis (Quinn *et al*., 1994).

Dimorphism of Emmonsia spp. is a possible reason for our findings of this microscopic fungi in mink liver (Hubalek *et al*., 1998). Larone (1995) testifed the ability of Emmonsia genus to generate pulmonic inflammatory process in rodents. The listed data support Hubalek (1998), whose studies show distribution of Emmonsia spp. thanks to small rodents, who are carriers of a pathogenic agent. Possibly, Emmonsia spp. penetrate into mink organism from the contaminated cage bedding.

Among all types of microscopic fungi found in mink liver there were 42% of Dematiaceous group fungi (Aureobasidium pullulans, Chaetomium spp., Cladosporium spp., Scedosporium spp., Wangiella spp.) (Ulloa, Hanlin, 2000; Kwon-Chung, Bennett, 1992). The common feature of these fungi is the presence of melanin in the cell wall. Other researchers (Zhdanova, Vasilevskaya, 1990) have proved that the presence of melanin pigment affects essentially the endurance of these cells against the influence of environmental moisture, temperature and radiation of the sun as well as providing vitality in the surroundings with an insufficient amount of nutrients. In addition, when in a body, the dark pigmented microscopic fungi containing melanin have an increased endurance against the body immunity protective factors.

With specific staining method in the formalin-embedded mink livers we detected PAS – positive yeast-like fungi. We explain findings of microscopic fungi in perivenular area with an individuality of venous blood circulation in liver, because portal veina is divided in venous capillary, which flow together, establish liver veins (Junqueira *et al*., 1998). Contamination with microscopic fungi of periportal area we explain with research data of Scherr and Weaver (1953), who reported, that the necessity of oxygen for Y (yeastlike) forms is 5–6 time higher than M (micelial) forms of microscopic fungi. Our findings of yeastlike forms in bile ducts is confirmed by other scientists (Jubb *et al*., 1993), who report that mycotic pathogenic agents often contaminate bile ducts, while pathogenic agents can not be detected in blood circulation and in viscera.

Despite the large amount of mycologically detected microscopic fungi in mink liver, our research shows a small quantity of fungal yeastlike cells and hyphae. Possibly, our results suggest, that any staining of histological preparation does not provide uniform staining of all microscopic fungi in tissues. Relatively new cells of microscopic fungi, which contain a large amount of chromatin, are better stained with alkali contained stains, but older forms, which contain a small amount of chromatin, are better stained with acid containing stains (Feier *et al*., 1966).

Aleutian disease viruse and mediators of inflammation induced damage of blood vessels and increased its permeability (Zharov et al., 2003), as a result microscopic fungi can disseminate via blood vessels in to body. Vascular endothelial growth factor is one of the powerful moderators of endothelial permeability (Esser *et al*., 1998; Nolan *et al*., 2004), which promotes blood vessels disruption, increases permeability and development of inflammatory process (Taniguchi *et al*., 2001). VEGF can be produced by various cell types – macrophages, blood platelets, leukocytes, PMN neutrophils (Thomson, Lotze, 2003; Coenjaerts *et a*l., 2004). Consequently, VEGF is expressed from periportal hepatocytes in areas of the liver, which are richly supplied with oxygen. Thus we suggeste on VEGF support to sinusoidal endothelial cells and hepatocytes to proliferate during renascence of liver sinusoids. Our assumption is supported by the investigations of other scientists (Taniguchi *et al*., 2001; Shimizu *et al*., 2005). Nevertheless, also other authors (Shimizu *et al*., 2005; Hironobu *et al*., 2006; Osada *et al*., 2006; Tsuchihashi *et al*., 2006) suggested, that only hypoxia stimulated VEGF expression.

Finding VEGF in periportal area explains the location of Kupffer cells in this area. Kupffer cells are an important producer of VEGF (Taniguchi *et al*., 2001).

Our research does not suggest a positive relation between inflammation cells and intensity of VEGF expression, which confirms persistence of the agent with an impact on VEGF. As it turns out, the Parvoviridae viruses demonstrate oncosuppressive activity and are blocking to VEGF activity (Blechacz, Russell, 2004).

Hepatocyte growth factor (HGF) in normal hepatocytes persist in a non active form (Defrances *et al*., 1992; Miyazawa *et al*., 1996; Ishikawa *et al*., 2001). In case of liver damage or irritation, HGF is transformed in to active form and hepatocytes become immunohistochemically able to respond with anti-HGF antibody (Ljubimova *et a*l., 1997).

Our results of HGF expression in cytoplasma of hepatocytes is supported by Thomson and Lotze (2003). Recognized dispersion of HGF in our research, mainly around bile ducts and portal tracts, fall within areas, where we mainly establish inflammation and the presence of microscopic fungi, because HGF stimulates not only the proliferation of liver parenchyma, but also the proliferation of biliar epithelial cells (Joplin *et al*., 1992). HGF in liver can also be produced by non parenchymal cells, for example, hepatic stellate cells, Kupffer cells, sinusoidal endothelial cells (Lindroos *et al*., 1991; Maher, 1993). Between non parenchymal cells HGF expression we suggest in endotheliocytes of veins, which, possibly approves compensatory activity of HGF during inflammation. Thereby HGF operates as a factor, which promotes liver regeneration during damage (Ljubimova *et al*., 1997; Ishikawa *et al*., 2001; Watanabe *et al*., 2003; Hironobu *et al*., 2006).

Conclusions

In summary, we conclude, that the microscopic fungi can penetrate liver of mink infected with Aleutian disease. In spit of the infiltration of inflammation cells, VEGF and HGF intensive expression are indicating regeneration ability of the mink liver.

Detection of VEGF and HGF simultaneously to inflammation liver might be connected to the tissue ischemia and damage realized by the same inflammatory cells.

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