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Chronic viral infections and development of vascular malformations of Head&Neck: is there a correlation?

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OBJECTIVES

Angiogenesis is the process of new vessels formation through growth factors, such as **vascular endothelial growth factor (VEGF**), that stimulate endothelial cells. These cells, once stimulated, organize themselves into tubular structures for the composition of new vessels and express specific surface proteins, such as **CD31**.[1] Several Authors showed that viral infections can determine new vascular structures onset, due to the expression of receptors that bind, and therefore stimulate, endothelial cells, or through the production of growth factors.

Hepatitis B virus (HBV) can be related to the development of hepatic vascular malformations or benign tumors, such as hemangioma, or even to hepatocarcinoma and cholangiocarcinoma.[2] But can a chronic viral infection determine the development of vascular malformations/tumors also in other body districts, such as **Head and Neck**? To answer this question, a case of a 52 years old woman with chronic HBV infection is described.

METHODS

The patient presented **a lesion of the right upper lip**, confirmed by instrumental ultrasound examination, clinically with hard consistency, a size of approximately 1.5cm, not painful and covered by normal mucosa.

The patient had been affected by **chronic viral hepatitis B** since the age of 13 years old; virological serum tests reported the following values: HbsAg of 0.051 UI/ml, HBsAb <3.10 mIU/ml, HBV-DNA viral load of 174 UI/ml (Table 1).

The lesion was surgically excised and histologically analyzed. Macroscopic examination showed a brownish fragment of 2x0.5 cm of hard consistency; the microscopic analysis showed a proliferation of **large-caliber vessels with thickened muscle tunic, surrounded by small vessels**. The immunohistochemical investigation showed that the endothelial cells of these vessels were **podoplanin negative** and **CD31 positive**. The histopathological diagnosis resulted in **"arteriovenous malformation."** (Figure 1)

GRAPHS AND TABLES

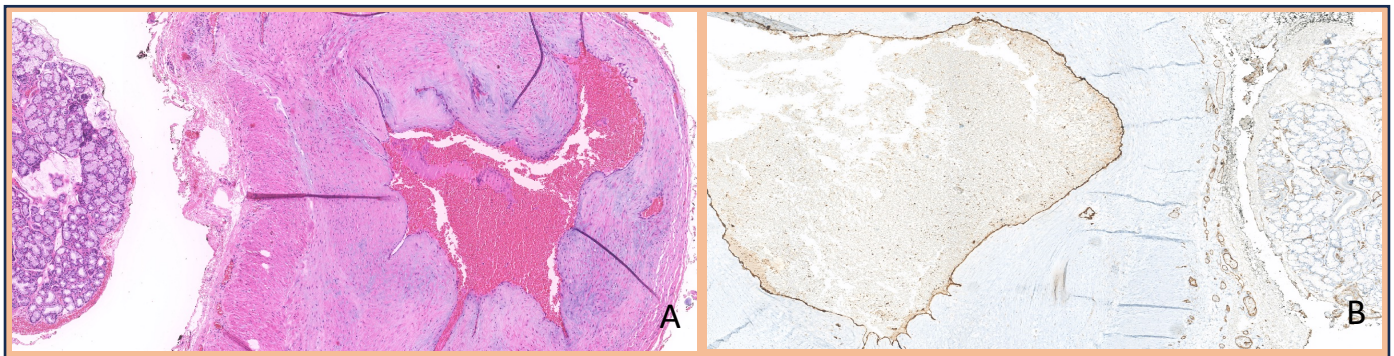

Fig 1. Poorly defined vascular proliferation of dilatated huge channels with thick medial layer (A, H&E 5x) resulted IHC-positive for CD31 (B 5x)

Antigens (Ag)/Antibodies (Ab)	Patient's Values	Reference Values
HBsAg	+	Negative
HBsAgq (quantitative)	0.051 IU/ml	<0.030-60000
HBsAb	<3.10 IU/ml	<10 negative; >10 positive
HBcAb	+	
HBeAb	+	
HBV DNA	**174 IU/ml**	Negative

Table 1. Patient's virological picture of chronic Epatitis B infection. In Table, the patient's values and the values of references (indicated in actual guidelines) are reported. UI= international unit; ml= milliliters

RESULTS AND DISCUSSION

In chronic HBV patients there is evidence of altered vascular architecture with formation of new tubular vessel-like structures with CD31positive endothelial cells. Several Authors have shown that VEGF is an important angiogenic factor implicated in the development of HBV-related hepatocarcinoma.[1] Studies on the HBV genome show that **hepatitis B viral protein X (HBx)** is the main inducer of VEGF expression in HBV-related hepatocarcinoma.[3] HBx is a regulatory protein, involved in the processes of transcription, stress response, protein degradation and cell signaling.[4] HBx activates the mitogen-activated protein kinase (MAPK) pathway, resulting in increased 'expression of angiopoietin-2 (Ang-2) and stabilization of hypoxia-inducible factor 1a (HIF-1a). HIF-1 activation, due to direct binding of HBx, correlates with tumor growth and survival as well as tumor angiogenesis, by directly stimulating VEGF expression.[3,4] Chronic HBV infection is also characterized by the persistence of **hepatitis B virus surface antigen (HBsAg);** Shu-Xiang Wu et al report that HBsAg plays a key role in angiogenesis in chronic HBV patients by directly stimulating VEGF and promoting neovascularization.[5] Thus, both HBx and HbSAg are important stimulators of angiogenic processes through direct stimulation of VEGF, so the hypothesis formulated by the Authors is that in patients with chronic HBV infection with a viral load > zero, the virus still has the ability to circulate in the blood and determine neoangiogenesis processes outside the liver. Probably the Head and Neck district may be affected by the neoangiogenesis due to the dense vascularization by small vessels, which are usually the most involved in the process.

CONCLUSION

Describing this case, the Authors formulated the hypothesis of correlation between chronic HBV infection and development of Head&Neck vascular malformation. The interesting element is the presence in the sample of mature endothelial cells positive for CD31, that is an endothelial surface protein closely related to stimulation by HbsAg. This is a preliminary hypothesis and further studies with larger samples and more specific molecular tests are needed to confirm it. However, reporting the possibility of this correlation is important to lay the foundations to carry out new molecular scientific research on the topic.

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