Human Pathology 165 (2025) 105934

Contents lists available at ScienceDirect

Human Pathology

journal homepage: www.elsevier.com/locate/humpath

GNAQ-/GNA14-mutated hepatic vascular malformation with capillary proliferation in adults and children

Anne Kristin Fischer [a,*], Carina Heydt [a], Janna Siemanowski-Hrach [a], Vedat Alibegovic [b], Kathrin Hauptmann [c], Christian Vokuhl [d], Reinhard Büttner [a], Hans-Peter Fischer [d,e]

[a] Institute of Pathology, University of Cologne, Kerpener Str. 62, 50937, Germany
[b] Institute of Pathology, Ordensklinikum Linz Barmherzige Schwestern, Seilerstätte 4, 4010, Linz, Austria
[c] Institute of Pathology, Charité Campus Mitte, University of Berlin, Virchowweg 15, 10117, Berlin, Germany
[d] Institute of Pathology, University of Bonn, Venusberg Campus 1, 53127, Bonn, Germany
[e] Medical Care Centre of Pathology and Cytology, Troisdorf, Mendener Straße 12, 53840, Troisdorf, Germany

ARTICLE INFO

Keywords:
Congenital hepatic vascular malformation associated with capillary proliferation
GLUT1 negativity
GNAQ/GNA14 mutation
Vascular malformation

ABSTRACT

Aims: Congenital hepatic vascular malformation with capillary proliferation (HVMCP) is a rare pseudotumourous liver lesion, to date only known in children. Diagnostic pitfalls in infant and, for the first time, in adult cases are histomorphologically characterised and molecularly analysed on driver mutations playing a role in angiogenesis and angioproliferation.

Methods and results: We histomorphologically characterised 4 early childhood and 2 adult cases, which showed malformed venous, cavernous and dissecting CD34-positive, GLUT1-negative capillary formations, followed by trabecular disarrangement of the involved liver parenchyma. As shown exemplarily, infant cases can lead to misdiagnosis as Glypican 3-positive hepatoblastoma. In adults, broadened capillarized liver trabecules might imitate hepatocellular carcinoma and dense capillary formations can resemble endothelial tumours, particularly hepatic small vessel neoplasia. In all cases, vascular malformation was the diagnostic key feature. Custom hybrid-capture-based sequencing assays were conducted, covering a broad range of genes active in angiogenesis and angioproliferation. Of the cases, 3, including 1 adult case, showed pathogenic activating driver mutations in *GNAQ/GNA14*. One adult lesion proved to be wild-type. Two wedge biopsies did not allow for molecular analysis.

Conclusions: HVMCP has to be differentiated from true vascular neoplasms, particularly from hepatic congenital haemangioma, hepatic infantile haemangioma and hepatic small vessel neoplasia but also from solid malignant hepatocellular tumours. Recognition of the underlying vascular malformation might disclose the pseudotumourous nature even in biopsies. Detection of driver mutations in the Gqα-protein-coding gene family with activation of the downstream MAPK/ERK pathway may open up a future treatment option for non-resectable lesions with MAPK/ERK inhibitors.

Clinical trial number: Ethic Votum BioMaSota No.13-091.

1. Introduction

Congenital hepatic vascular malformation with capillary proliferation (HVMCP) is a rare tumour-like, congenital vascular lesion, observed in early childhood. There exist no studies on its incidence. Mo et al. [1] first described it in 2004. To date, it is neither listed in the current WHO classification of digestive system tumours [2] nor paediatric tumours [3], nor in the recent ISSVA classification for Vascular Anomalies from 2025 [4]. However, it is a well-known tumorous malformation in hepatopathology and paediatric pathology, and listed in the current MacSween's Atlas of Liver Pathology [5] (see Fig. 6).

HVMCP is mostly diagnosed through prenatal ultrasonography or in the early weeks or months after birth when clinical symptoms arise. It presents as an intrahepatic mass with accompanying abdominal distension, hepatomegaly, cardiomegaly and anaemia. Radiologically, dilated hepatic arteries and portal veins associated with the lesion are reported [1]. Rarely, severe thrombocytopenia and fibrinolysis with disseminated intravascular coagulopathy occur according to

* Corresponding author. Institute of Pathology, University of Cologne, Kerpener Str. 62, 50937, Cologne, Germany.
E-mail address: anne.fischer1@uk-koeln.de (A.K. Fischer).

https://doi.org/10.1016/j.humpath.2025.105934
Received 7 July 2025; Received in revised form 6 September 2025; Accepted 9 September 2025
Available online 12 September 2025

Kasabach-Merritt syndrome (KMS). Ultrasonography may show a solitary liver mass with large areas of central infarction, haemorrhage and calcification, surrounded by abnormally dilated blood vessels corresponding to an arterio-venous malformation.

Histomorphologically, as initially defined by Mo et al., HVMCP represents a vascular malformation characterised by a trizonal structure with a regressive centre, a transition zone of malformed dilated blood vessels, and a nodular capillary proliferation associated with disarranged liver parenchyma in the periphery [1]. For diagnosis of HVMCP, it is essential to demonstrate the three-zonal architecture and large, distorted and malformed blood vessels in biopsies and wedge biopsies, to distinct it especially from GLUT1-negative, *GNAQ*- and *GNA11*-mutated hepatic congenital haemangioma (HCH), one of its most important differential diagnosis [6–10]. Immunohistochemically, endothelial cells of the lesion are completely negative for glucose transporter-1 (GLUT1), a downstream target of hypoxia-inducible factor-1-alpha (HIF-1α). This finding contrasts with GLUT1-positive hepatic infantile haemangioma (HIH), another main differential diagnosis in paediatric hepatopathology [11–13]. Furthermore, the distinction from hepatic small vessel neoplasia (HSVN) can be challenging and demands thorough interdisciplinary examination [14–16]. However, in contrast to HVMPC, HSVN can occur multifocally and disseminate in rare cases [17]. Rarely, HVMPC can mimic hepatoblastoma and hepatocellular carcinoma (HCC).

To date, HVMCP has neither been documented in adult patients nor characterised at the molecular level. In this study, for the first time we bring together HVMCP in different age groups with mutations in genes from the Gqα-protein-coding gene family. This permits a deeper understanding of this very special type of basically vascular malformation that might be relevant for its classification and differential diagnosis against other vascular and solid liver lesions in adults and children, particularly HIH, HCH, HSVN, hepatoblastoma and HCC.

2. Material and methods

2.1. Ethics statement

The Institutional Review Board (IRB) of the University Hospital of Cologne approved the experiments. Informed consent was obtained from all patients whose tissue samples were included in the study (Ethic Votum BioMaSota No.13-091).

2.2. Cohort, clinical data, follow up

The collective of this multicentre diagnostic histopathological study comprised 8 cases of 3015 continuously recorded, non-selectively included resection and wedge biopsy cases from our consultant surgical pathology files in a time period of 16 years (Department of Pathology, and Section of Paidopathology, University Hospital of Bonn, Institute of Pathology & Cytology, Medical Care Centre Rhein-Sieg, Germany). It included formalin-fixed, paraffin-embedded tissue from liver explants, resection specimens, and wedge biopsies (Table 1). The collective consisted of 4 infants and 2 male adult patients with histopathologically confirmed HVMCP. The lesions were morphologically characterised according to the initial description by Mo et al. [1] The adult samples were treatment naïve prior to surgical resection and clinically suspected of HCC. One of the infant lesions (case 4) was first diagnosed on a wedge biopsy as hepatoblastoma and treated with one cycle of chemotherapy before resection (Table 1). In comparison, 2 vascular malformations with multiple macroregenerative FNH-like nodules without capillary proliferation including one case with hereditary haemorrhagic teleangiectasia (HHT) from adult patients were added and molecularly analysed.

Radiologic imaging of the lesions with documentation of growth/involution rate was mostly not accessible, since most cases were reference cases sent for tertiary consultation, partly from other states. However, in case 4, first suspected of hepatoblastoma, initial and post-chemotherapeutic size of the lesion was reported to be equal, with no tendency of growth or involution. This follow-up leads to overthink the diagnosis, with a re-biopsy and final resection. The premature infant (case 3) died short after biopsy due to renal failure. Both adult lesions were incidentally discovered by routine examinations and resected soon after since they were suspicious of HCC.

Only in case 1 of a 2-month-old girl, preoperative MRI imaging was provided (Fig. 1).

In none of the cases, vascular lesions outside the liver or a positive family history of vascular lesions were reported. As far as we now, there was not any intrauterine exposure to teratogens or toxins in the children's cases. In the adult cases, no benign or malignant neoplasms were reported. Patient anamnesis was negative for excessive alcohol uptake

Table 1
Clinical presentation, material, molecular-pathologic findings regarding HVMPC and 2 added vascular malformations without capillary proliferation (molecularly proven HHT (case 7) and 1 wild-type vascular malformative lesion (case 8)).

Case No.	Sex, Age	Diagnosis	Clinical Presentation	Localisation	Size	Specimen	Molecular Pathology
1	F, 2 m	HVMCP	Large, bulging mass exceeding into the abdomen with smooth borders suspected of rhabdoid tumour or hepatoblastoma. No relapse after 5 years.	Segment I/IV	11.5 cm	Small wedge biopsy	n/a (Coverage too low)
2	F, 3 m	HVMCP	Premature infant with large, bulging liver mass extending into the abdomen. No relapse after 5 years.	Segment IV/V	n/a	Small wedge biopsy	n/a (Coverage too low)
3	M, 1 m	HVMCP	Premature infant (33 + 4). Clinical diagnosis: postnatal haemangioendothelioma, hemodynamically relevant. Renal failure and exitus letalis 20 days after birth.	Subcapsular localisation	n/a	Small wedge biopsy	*GNAQ* (p.Q209H)
4	F, 8 m	HVMCP	Clinically suspected hepatoblastoma with elevated AFP. After diagnosis of hepatoblastoma on wedge biopsy neoadjuvant chemotherapy, 3 m later hemihepat-ectomy. No relapse after 15 years.	Right liver lobe	8.0 × 5.0 cm	Wedge biopsy, hemihepa-tectomy	*GNAQ* (p.Q209L)
5	M, 27 y	HVMCP	Incidentally detected, suspected of HCC. No relapse after 5 years.	Segment IVb	2.0 × 1.4 cm	Resection	*GNA14* (p.Q205L)
6	M, 42y	HVMCP	Incidentally detected, suspected of HCC. No relapse after 2 years.	n/a	3.2 cm	Resection	wt
7	F, 46 y	HHT with FNH-like macro-regenerative nodules	n/a	Both liver lobes	multiple nodular lesions up to 1.5 cm	Liver transplant	*ACVRL1* (p. Glu83SerfsTer39)
8	M, 59 y	Vascular malformation with FNH-like nodules	n/a	Complete adult liver	Ca. 20 cm	Liver transplant	n/a

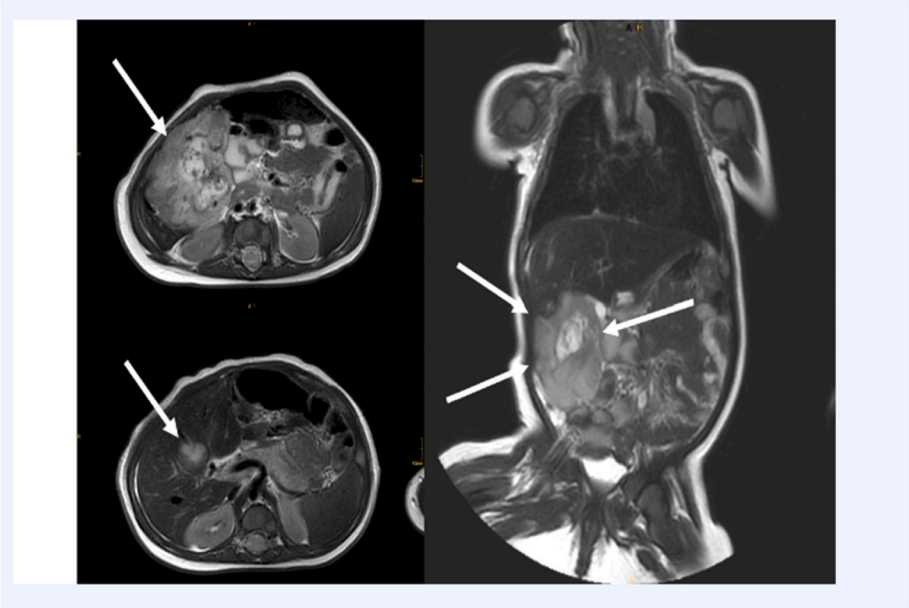

Fig. 1. Radiologic findings (MRI) of an 11.5 cm measuring HVMCP (arrows) in liver segments I/IV of a 2-month-old girl (case 1).

or drug abuse. No relapse of disease was reported in 15 years (case 4), in 5 years (cases 1–3, 5) and in 2 years (case 6) after resection (Table 1).

2.3. Samples

Formalin-fixed, paraffin-embedded specimens were used for diagnosis and further immunohistochemical and molecular analyses. In 5 cases, complete resection or (hemi)hepatectomia specimens were available. In 3 cases analyses were conducted on wedge biopsies not followed by resection.

2.4. Conventional histological and immunohistochemical analysis

Reference pathologists critically reviewed all cases for liver pathology and for paediatric oncologic pathology. Histopathological diagnosis was made using conventional staining methods (H&E, PAS, Elastica van Gieson, Gordon, Sirius, iron staining on serial slides). Tissue fragments 2–3 µm thick were cut from paraffin blocks and mounted on Superfrost slides (Menzel Gläser, Brunswick, Germany). After deparaffinization with xylene and gradual rehydration, antigen retrieval was achieved by pressure cooking in 0.01 mmol/L citrate buffer for 5 min. The slides were incubated with the respective monoclonal antibodies, counterstained with haematoxylin and mounted in an aqueous medium. Immunohistochemical characterisation of the endothelia was performed using antibodies against CD34 (Cellmarque/CE, QB End10, 1:700, Citrate), CD31 (Dako/CE, JC70A, 1:200, Citrate), D2-40 (Covance/CE, D2-40, 1:100, no dilution), ERG (Cellmarque/CE, EP111, 1:300, EDTA) and GLUT1 (Cellmarque/CE; polyclonal, 1:400, EDTA). The smooth-muscle vessel wall was visualized through SMA (Dako/CE, 1A4, 1:1000, EDTA), proliferation by Ki67 (ZetaCorp/CE, MIB1, 1:200, EDTA). The hepatocytes were analysed for the expression of Glypican-3 (Cellmarque/CE, 1G12, 1:50, EDTA). Staining was performed semi-automatically using a Ventana Benchmark Ultra immunostainer.

2.5. Molecular analysis

Analysis of variants was conducted with a special custom gene panel covering a broad range of genes that play a role either a role in liver carcinogenesis or in vasculogenesis and carry already known mutations in other vascular malformations. The list of genes our panel covered is depicted in Supplementary Table 1.

2.6. DNA extraction

For parallel molecular deep sequencing analysis (next-generation sequencing), DNA was extracted from the vascular lesions and from the background liver tissue $\geq$1.0 cm away from the lesion. Tissue from one representative paraffin block was macrodissected (using two to three 10-µm sections). DNA was extracted using the Maxwell RSC FFPE Plus DNA Kit (Promega) Kit (Promega, Mannheim, Germany) on a Maxwell RSC (Promega) following the manufacturer's instructions.

2.7. Custom hybrid-capture-based sequencing assays

DNA was first quantified using the Tecan Trading AG (QuantiFluor dsDNA system, Männedorf, Switzerland). After enzymatic fragmentation within a suitable range, library preparation and enrichment, a customized Twist bioscience panel was used following the manufacturer's instructions (Twist Biosciences, CA, USA) (Supplemental Table 1 – Genlist). Post-enriched libraries were sequenced on a NextSeq 500 or NovaSeq (Illumina Inc., San Diego, CA, USA). Sequencing data were analysed using an in-house pipeline. A 5 % cutoff for variant calls and a minimal coverage of >200 × were used for data interpretation.

3. Results

Clinical data, material, macroscopic features and molecular findings are listed in Table 1.

3.1. Macroscopic features

Resected cases of HVMCP were solitary, nodular lesions with blurred borders. One resected infant lesion measured 8.0 × 5.0 cm in diameter; the other resected infant lesion measured 11.5 cm. The lesions of the 2 adult male patients measured up to 3.2 resp. 2.0 cm in diameter (Table 1). The large lesions showed a 3-zone architecture with a) a central regressive zone with gross calcifications and broad, radiating fibrotic septa; b) an intermediate zone with large blood vessels and nodular transformed liver parenchyma with interspersed fibrotic septa; and (c) a peripheral spongy zone with nodular disarranged liver parenchyma (Fig. 2). The lesions developed in normally appearing liver parenchyma. Both added lesions of adult patients without capillary proliferation consisted of macro-regenerative nodules similar to FNH in

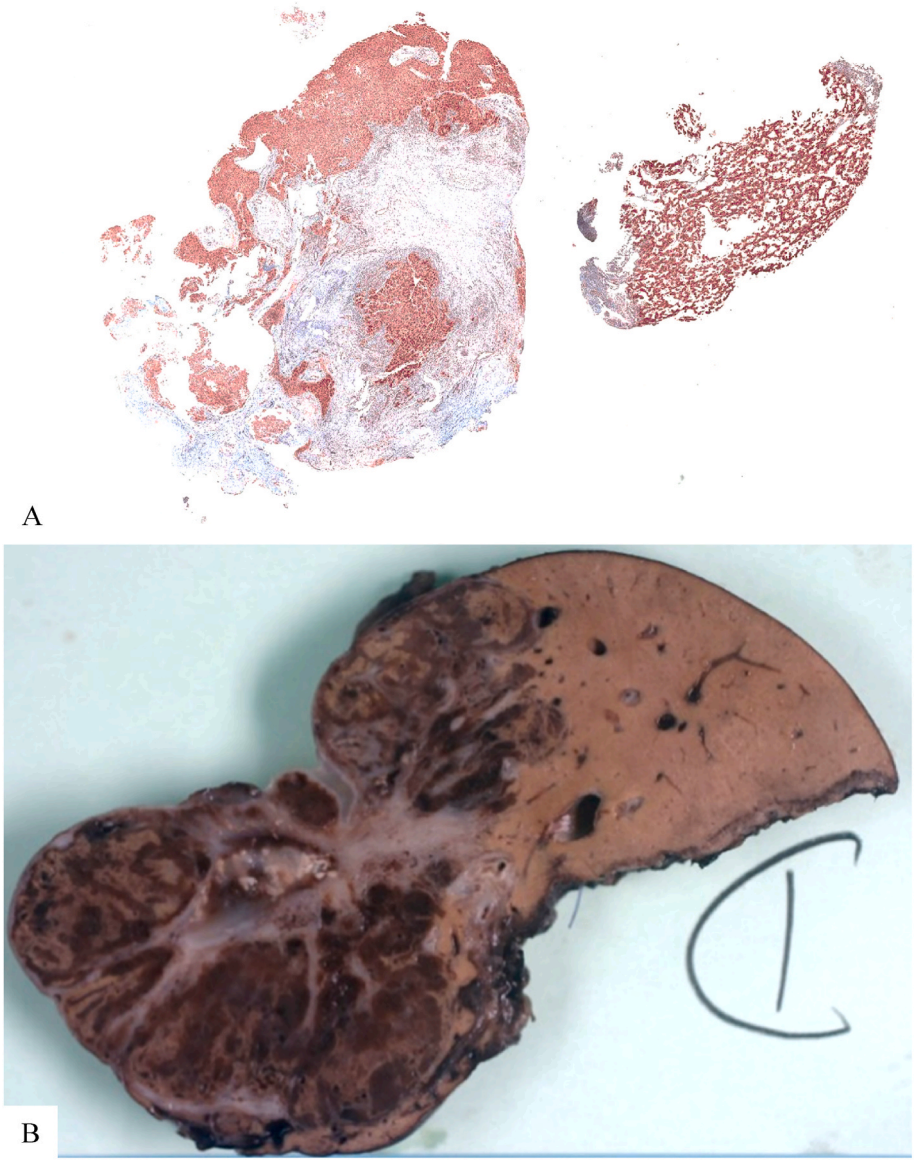

Fig. 2. Congenital hepatic vascular malformation with capillary proliferations in an 8-month-old infant (Case 4): (A) Wedge biopsy from the lesion with a positive reaction for Glypican 3. (B) Cross-section through the resection specimen 3 months after 1 cycle of chemotherapy. Depiction of the trizonal architecture with a central regression zone with coarse calcifications. Large pathologically structured ectatic vessels in the intermediate zone and a spongy solid, nodularly transformed periphery.

an area up to 10 resp. 20 cm.

3.2. Histologic and immunohistochemical features

Basically, all cases of HVMCP presented focal vascular malformative lesions including venous-like, arterial, cavernous blood vessels as well as ectatic and densely packed capillary formations associated with disarranged liver parenchyma. Liver tissue outside the lesions appeared inconspicuous. Even the wedge biopsies of the infants contained irregular thin-walled malformed anastomosing vessels (Fig. 3A). Central parts of the large resection specimen included regressive fibrosis and calcifications. The smaller adult lesions comprised cavernous malformed vessels (Fig. 4A and B). Next to them, prominent capillaries surrounded broadened liver trabecules, giving the impression of a primary hepatocellular neoplasm (Fig. 3B and C; Fig. 4C and D). Remarkably, in the wedge biopsy of the 8-month-old child, taken after the first cycle of chemotherapy, the hepatocytes in the vascular lesion and those in the surrounding liver parenchyma both reacted intensely with Glypican-3 (Fig. 2A). These findings gave reason for the primary diagnosis of a foetal hepatoblastoma. Capillaries were lined with monolayered endothelial cells with slightly prominent roundish nuclei (Fig. 3C). The intermediate and outer parts of the lesions contained closely packed capillary proliferations dissecting the liver parenchyma (Fig. 3D and 4D). Isolated bile ducts (Fig. 4D and E), large isolated arteries and accompanying veins without bile ducts (Fig. 4D–F) underline that portal structures were part of the malformative process. Immunohistochemically, CD34 (Fig. 3D; Fig. 4E and F), CD31 and Erg highlighted the vascular nature of dilated blood vessel channels and capillaries. GLUT1 was not expressed in any lesion (Fig. 3E and 4G). Only few Ki67-positive nuclei revealed the low proliferative activity of the capillary proliferates and bystander cells (Fig. 4H). The intensely Glypican 3-positive infant case reacted only weakly with this antibody 3 months after the initial wedge biopsy (Fig. 3F). The intra- and extra-lesional liver parenchyma of the adult cases was negative for Glypican-3.

The added vascular malformations without capillary proliferation consisted of pathological thick- and thin-walled anastomosing vessels

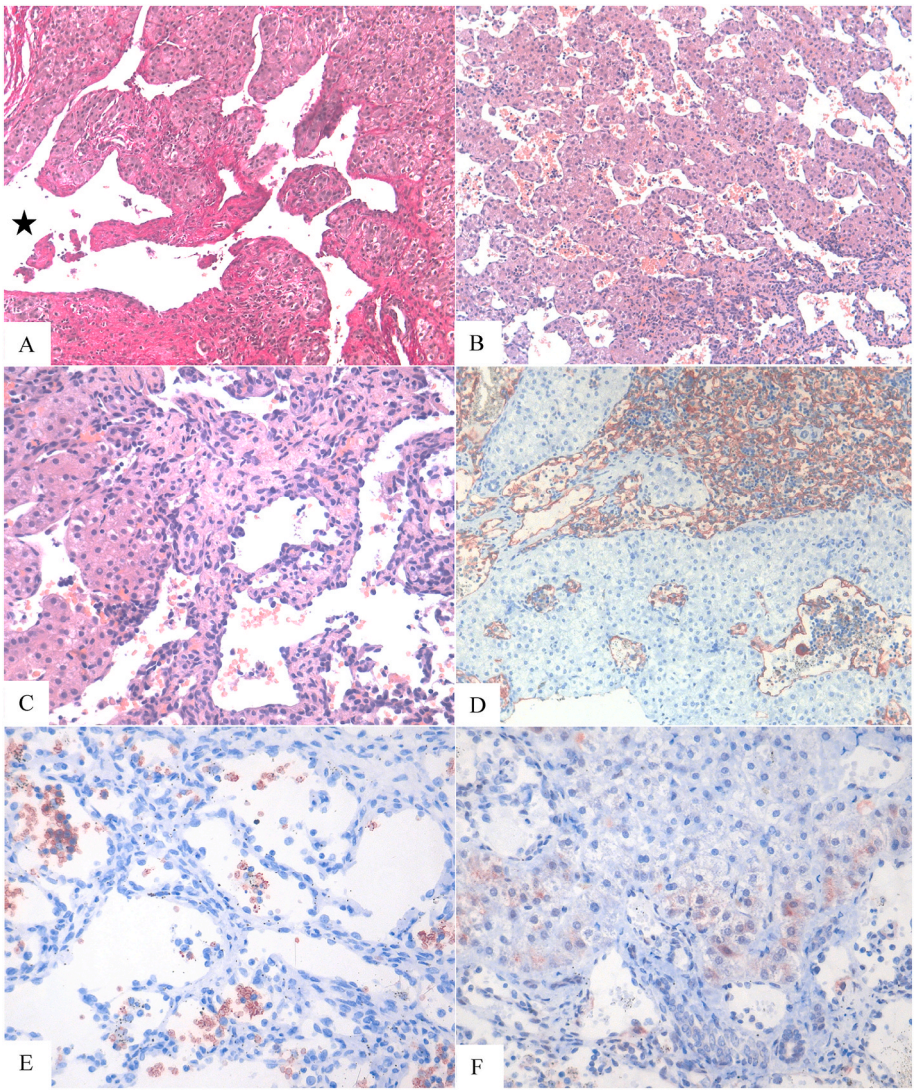

Fig. 3. Congenital hepatic vascular malformation with capillary proliferation in an 8-month-old infant: (A) Irregular, partially cavernous, thin-walled malformed anastomosing blood vessels in the centre of the lesion (asterisk) (EvG). (B) Broad liver trabecules imitating a foetal hepatoblastoma between anastomosing ectatic capillaries. (C) Capillary endothelial cells with slightly prominent roundish nuclei. (D) Densely packed CD34-positive capillaries dissecting the liver parenchyma. (E) GLUT1-negative capillaries. (F) Only few weekly Glypican 3-positive hepatocytes 3 months after wedge biopsy.

interconnecting with sinusoidal ectasias. In contrast to the HVMPC cases, they were associated with a disarranged lobular architecture of the liver parenchyma and macroregeneratory nodules with characteristics of focal nodular hyperplasia.

3.3. Molecular pathologic findings

We detected a post-zygotic missense mutation in *GNAQ* at glutamine 209 (p.Q209L) in the small-capillary components in 2 infant lesions (case 3 and 4) and a corresponding mutation in the paralogous gene *GNA14* (p.Q205L) in the small-capillary component of the adult lesion (case 5) (Fig. 5). Low coverage did not allow for molecular analysis in two infant wedge biopsies (case 1 and 2) without a following resection. The second adult case of HVMPC (case 6) was a wild-type lesion (Table 1). One of the added vascular malformations with associated FNH-like macroregenerative nodules showed a to date unknown *ACVRL1* (*ALK1*) mutation (*ACVRL1* EX3: c.246del; p.Glu83SerfsTer39) according to HHT (case 7). The other one was a wild-type lesion in our analysis (case 8).

Mutations detected in subtypes of hepatic adenoma or playing a role in liver carcinogenesis like *hTERT*-promotor mutations or *CTNNB1* mutations (β-catenin) were not found (see Supplementary Table 1). Also, mutations in genes engaged in angiogenesis and angioproliferation or mutations already known from other vascular malformation syndromes (ie. pulmonal artery hypertension) were not detected.

4. Discussion

HVMCP is a rare, largely unknown and therefore rarely diagnosed benign vascular lesion of early childhood. To date, its molecular background is unexplored. For the first time, we describe 2 cases in adults and compare them with lesions in early childhood. We also conducted extensive molecular analysis to obtain further insight into the nature of these lesions. Clearly malformed thin-walled ectatic, irregularly herniated and thick-walled stenosed venous and cavernous vessels, accompanied by large arteries, represent the basic vascular malformation. It is combined with more peripherally sited, densely capillarized areas which penetrate and dissect the surrounding liver parenchyma. Apart from the underlying tissue, HVMCP morphologically resembles angiomatosis resp. diffuse haemangioma of soft tissue, which also becomes symptomatic in infancy. Nevertheless, if not diagnosed and resected in childhood, HVMCP will likely also be primarily observed in adulthood,

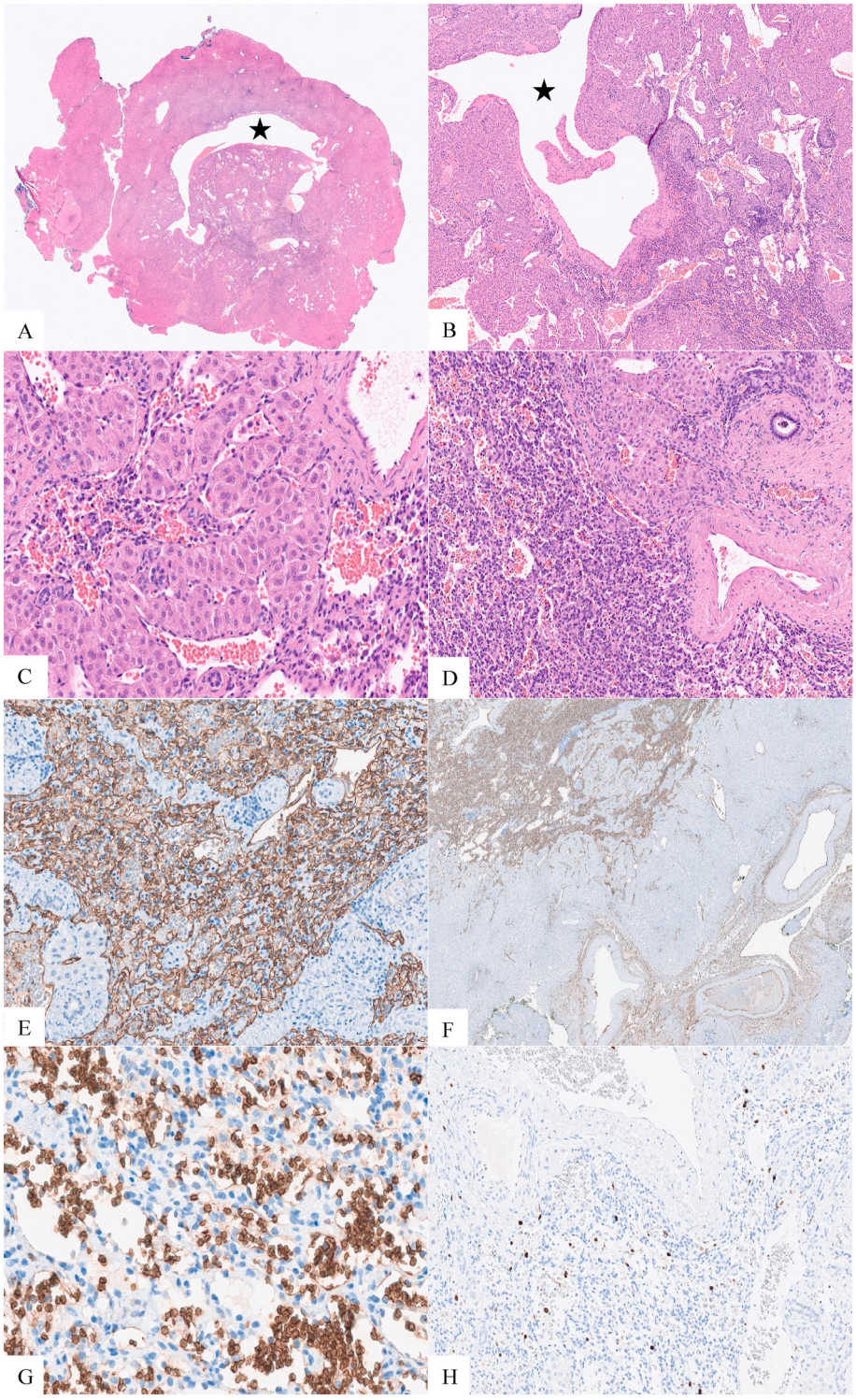

Fig. 4. Microscopic and immunohistochemical aspects of a congenital hepatic vascular malformation with capillary proliferation in an adult male patient (case 5): (A) Overview demonstrating a malformed thin-walled cystic blood vessel in the centre of the lesion (asterisk). (B) Large, pathologically malformed cavernous blood vessels (asterisk) with incomplete media underlining the malformative character of the lesion. (C) Capillary proliferation dissecting the liver parenchyma and a malformed portal field with an isolated bile duct and an isolated artery (right). (D) Irregularly running broadened liver plates of disarranged liver parenchyma are imitating a hepatocellular neoplasm; prominent capillaries are imitating an endothelial tumour. (E) Strong immunohistochemical CD34 expression of densely packed capillaries, here resembling hepatic small-vessel neoplasm. Isolated bile ducts (asterisk) underline that portal structures are part of the malformative process. (F) Large isolated arteries (asterisk) and accompanying vein (arrow) without bile duct underline the malformative process (CD34) (G) Capillaries are negative for GLUT1. GLUT1-positive erythrocytes in the capillary lumina serve as an internal positive control. (H) Low proliferative activity of the capillary proliferates and bystander cells (Ki67).

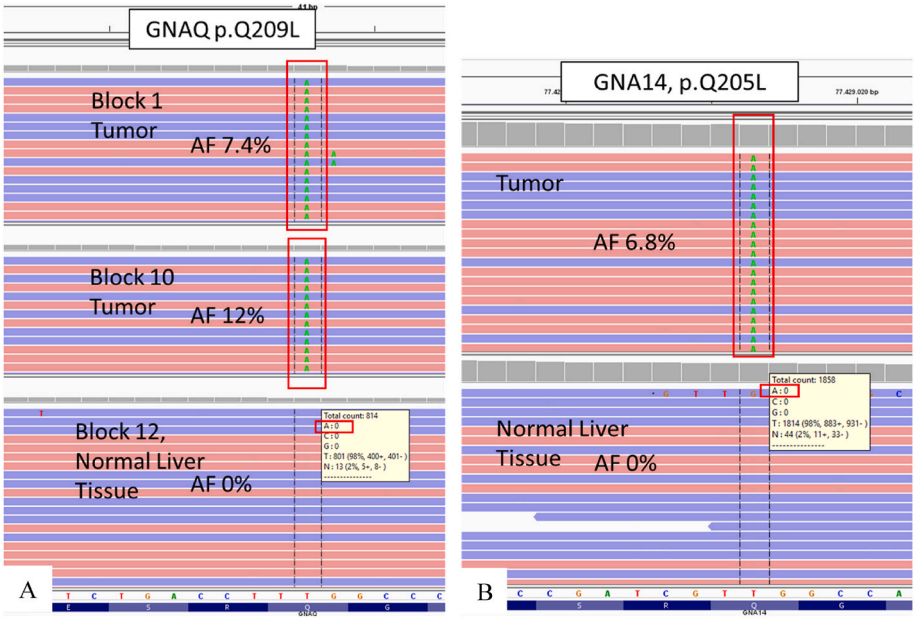

Fig. 5. Molecular analysis of HVMCP demonstrating a hyperactive postzygotic activating somatic mutation in *GNAQ* at glutamine 209 (p.Q209L) in an infant lesion (case 4) and an analogous mutation in *GNA14* (p.Q205L) in an adult lesion (case 5).

as we demonstrated in 2 of our cases. Its characteristic histomorphology combined with a broader age spectrum also justifies a more extensive differential diagnosis of HVMCP, particularly in biopsy material.

HVMPC are solitary lesions, in contrast to occasionally multifocal HIH [10–12]. GLUT1-positive HIH can resemble the monotonous compact capillary areas of HVMCP, which however do not react with this glucose transport protein. Central areas of large HVMCP might show extensive degenerative changes and do not regress completely, unlike in HIH. Furthermore, distinction from GLUT1-negative, rapidly or partially or non-involuting HCH (RICH or PICH or NICH) on biopsies is essential and demands thorough histopathological examination of the malformed blood vessels which characterise HVMCP. Fibrosis and malformed blood vessels can be observed particularly in central areas of the RICH, which can result in zonation in some of these lesions. However, especially our adult cases do not cover the definition of a rapidly involuting congenital haemangioma. The structural abnormalities demonstrated in our cases (large isolated arteries and accompanying veins without bile ducts and, on the other hand, isolated bile ducts without accompanying portal veins and hepatic arteries, demonstrated in Fig. 4, case 5, adult) show a basic malformative process including portal structures without additional signs of regression. This finding cannot be explained as a secondary phenomenon. It is possible that the mutation in *GNA14* detected here is a secondary event and the basis of the capillary proliferation on the primary malformation.

The intra-lesional liver parenchyma of HVMCP can form broader trabecules surrounded by a CD34-positive microvascular bed. This pattern might imitate a true hepatocellular neoplasm, in particular hepatoblastoma in infancy and hepatocellular adenoma or even well-differentiated hepatocellular carcinoma in adulthood. In doubtful cases, a further analysis of the hepatocellular component with immunohistochemical markers characterising HCA or HCC could be necessary. In infants, the intralesional liver parenchyma might retain its foetal character, as demonstrated by a significant Glypican-3- and glutamine synthetase-expression. This might explain the initial diagnosis of foetal hepatoblastoma in one of the infants' wedge biopsies. Nevertheless, the vascular malformation could be detected in the primary wedge biopsy; furthermore, the extra-lesional parenchyma reacted positive with this oncofoetal protein, which was nearly completely lost in the resection specimen 8 months later. The other cases of the study were negative for Glypican-3.

HVMCP should be differentiated from other malformative vascular lesions of the liver, such as hereditary haemorrhagic teleangiectasia (HHT; Osler-Weber-Rendu disease) (case 7). This generalized disease is characterised by arteriovenous anastomoses which are partly connected by ectatic sinusoids. It lacks capillary proliferation and is based on characteristic mutations in *ALK1/ACVRL1* c.314-35A > G (Activin receptor-like kinase 1/TGFβRI (TGFβ receptor ALK1)) and *ENG* c.207G > A (Endoglin/TGFβ1 coreceptor/TGFβRIII) (see below), as shown in one of our added lesions (Berg 1997) [18–21].

At first glance, cavernous haemangiomas and diffuse haemangiomatosis with anastomosing thin-walled vessels might imitate a true vascular malformation, particularly in peripheral areas or small satellite nodules [22]; however, capillary proliferation is lacking in these tumours. A prominent capillarization followed by pronounced or isolated liver plates can be found in the periphery of hepatic angiosarcoma. These tumours should be identified by atypical endothelial cells with large nuclei, high proliferative activity and overexpression of p53 [23].

In adult cases, HSVN is a relevant differential diagnosis. These rare solitary, poorly demarcated, unencapsulated tumours consist of thin-walled small capillaries lined by bland endothelial cells with horseshoe nail-like nuclei. The capillaries are embedded in a scant collagenous stroma including small hepatocytes and ductular structures, particularly in peripheral parts of the lesions [14–17]. These low-proliferative tumours are negative for p53 and GLUT1. In contrast to HVMCP, an underlying vascular malformation is missing.

HSVN and HCH are characterised by hotspot *GNAQ/GNA11*/GNA14 [5–7,10,17] mutations and, in case of HSVN, also by *PIK3CA* mutations [16]. This observation drew our attention to putative mutations in HVMCP that either play a role in angiogenesis and angioproliferation or encode proteins active in intracellular signal transduction. Indeed, in 3 of 4 analysable cases of HVMCP, we demonstrated an activating somatic mutation at glutamine 209 in *GNAQ* or at glutamine 205 in the paralogous gene *GNA14* in the capillary tumour component. Small wedge biopsies from non-resected infant cases did not allow for further molecular analysis. One adult HVMCP was a wild-type case. *GNAQ* and *GNA14* are over 90 % homologous, and they code for the q class of G proteins that transmit signals from G-protein-coupled receptors (GPCRs) to phospholipase C-beta (PLC-β) [24]. Activation of the GNAQ protein leads to hyperactivation of effector molecules, particularly PLC-β, mitogen-activated protein kinase (MAPK/ERG) and the KRAS signal

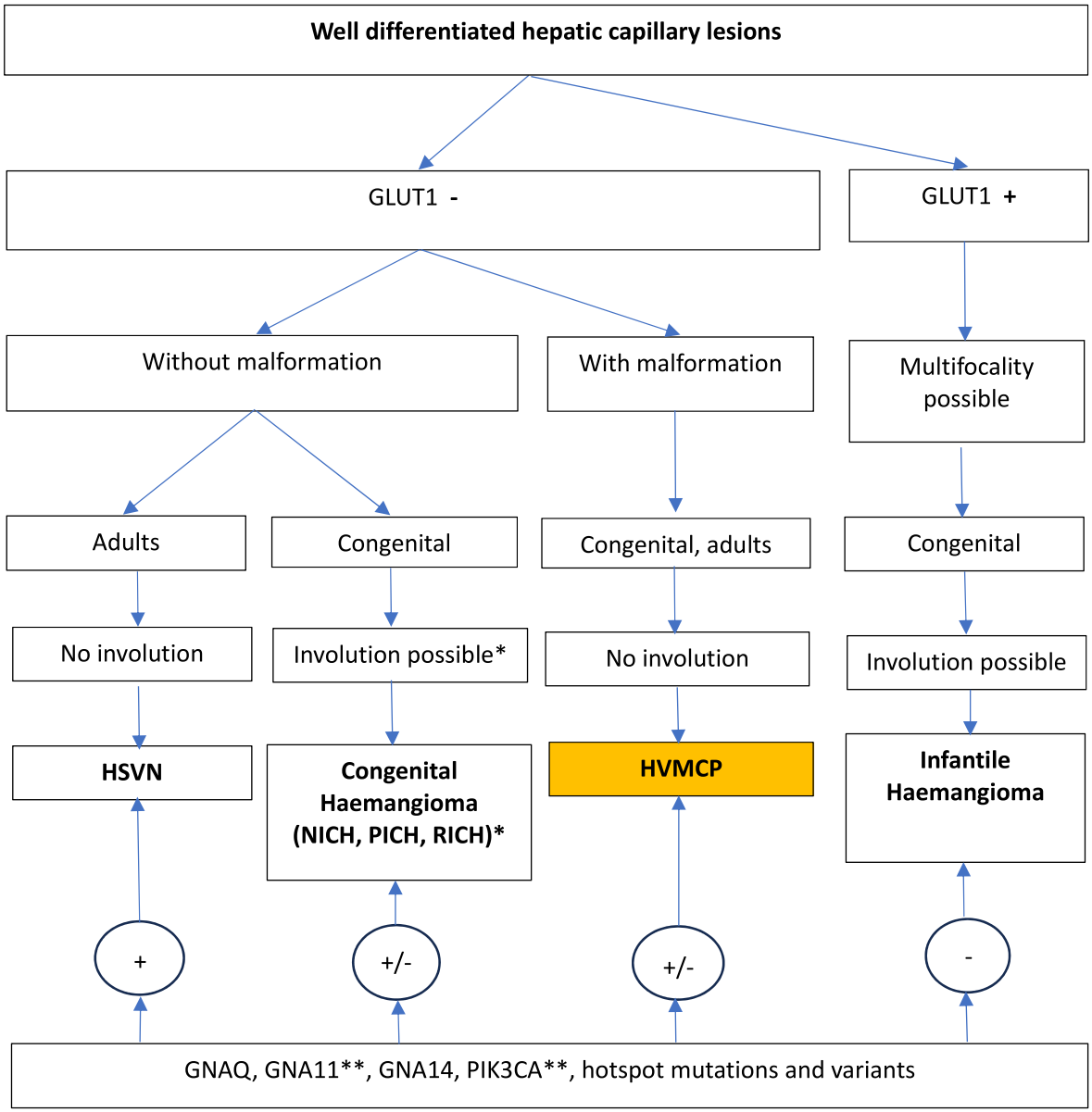

Fig. 6. Differential diagnostic algorithm for HVMCP versus other well differentiated hepatic capillary lesions.

pathway [25,26]. Schrenk et al. [25] demonstrated the effect of GNAQ activation on the formation of malformed capillary and venous vessels in the subcutaneous, visceral and brain tissue using mouse models whose concept of *GNAQ* mutation-driven vascular pathology could be transferred to the liver. Previous studies on dermal vascular lesions showed that these activating *GNAQ* mutations can be observed in congenital vascular tumours [27] and in syndromic lesions such as Sturge-Weber syndrome and port-wine stain nevus [28]. Therefore, our observation of activating *GNAQ/GNA14* mutations in a tumour-like congenital vascular malformation of the liver coincides with previously observed GNAQ-activated syndromic vascular lesions of the skin and consequently assigns HVMCP to the spectrum of mutation-driven vascular lesions. Furthermore, in a proof-of-concept mouse model, Schrenk et al. [25] demonstrated a clear effect of the MAPK/ERK inhibitor trametinib on the regression of pathological blood vessels and hyperproliferation, reduction of vascular permeability by disruption of VE-Cadherin expression in adherens junctions and hypercoagulation in initial preclinical studies [25]. HVMCP can be treated by liver resection. Recurrence of HVMCP after resection is not described in the few case reports [1,29] and not observed in our cases. The presence of *GNAQ/GNA14* mutations in very large and hemodynamically relevant HVMCP could in the future open up a new therapeutic concept for these lesions with MEK/ERK inhibitors as an alternative to surgical resection with a high intraoperative risk of morbidity or mortality.

5. Conclusion

In conclusion, we classify *GNAQ-/GNA14*-mutated HVMCP as a rare, focal tumour-like vascular malformation that we describe for the first time in adults. Given its clinical behaviour with partly pre- or perinatal existence and lack of involution in the course as well as its characteristic macro- and microanatomy, very large lesions can cause life-threatening hemodynamic complications, such as KMS. Furthermore, trabecular disarrangement of the involved liver parenchyma can lead to a clinicopathological misdiagnosis as hepatoblastoma in childhood cases. In contrast to infantile haemangioma of the liver, spontaneous involution is lacking. Lesions which were not discovered in infancy might present first in adulthood. In this context, HVMCP has to be differentiated from vascular neoplasms, particularly from *GNAQ-/GNA14*-mutated hepatic congenital haemangioma, hepatic small vessel neoplasia and solid

malignant hepatocellular tumours. The detection of driver mutations in the G-protein-coding genes with activation of the downstream MAPK/ERK pathway may open up a new future treatment option for non-resectable lesions with the MAPK/ERK inhibitor trametinib, which shows a promising effect on *GNAQ*-driven vascular lesions in the mouse model.

CRediT authorship contribution statement

Anne Kristin Fischer: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Carina Heydt:** Software, Formal analysis. **Janna Siemanowski-Hrach:** Software, Formal analysis. **Vedat Alibegovic:** Data curation. **Kathrin Hauptmann:** Data curation. **Christian Vokuhl:** Validation, Data curation. **Reinhard Büttner:** Validation, Supervision, Resources, Project administration, Formal analysis. **Hans-Peter Fischer:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Informed consent

Informed consent was obtained from the patients for the publication of their information and imaging.

Financial support statement

This work was founded by the Köln Fortune Foundation of the Medical Faculty of the University of Cologne, Germany.

Declaration of competing interest

The authors do not have any disclosures to report.

Acknowledgments

Dr Anne Kristin Fischer received funding from the Koeln Fortune Program, Faculty of Medicine, University of Cologne (Project No. 98/2023).

ABBREVIATIONS

DNA	Deoxyribonucleic acid
GLUT1	Glucose transporter 1
G-protein	Guanin nucleotide-binding protein
GPCR	G-protein-coupled receptors
FFPE	Formalin-fixed, paraffin-embedded tissue
FNH	Focal nodular hyperplasia
HCH	Hepatic congenital haemangioma
HHT	Hereditary haemorrhagic teleangiectasia
HIH	Hepatic infantile haemangoma
HVMCP	Hepatic vascular malformation with capillary proliferation
ISSVA	International Society for the Study of Vascular Anomalies
KSM	Kasabach-Merrit syndrome
KRAS	Kirsten rat sarcoma viral oncogene homologue
NICH	Non involuting congenital haemangioma
PAS	Periodic Schiff acid
PICH	Partially involuting congenital haemangioma
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
RICH	Rapidly involuting congenital haemangioma
RNA	Ribonucleic acid
SMA	Smooth-muscle antigen

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2025.105934.

References

[1] Mo JQ, Dimashkieh HH, Bove KE. GLUT1 endothelial reactivity distinguishes hepatic infantile hemangioma from congenital hepatic vascular malformation with associated capillary proliferation. Hum Pathol 2004 Feb;35(2):200–9.
[2] International Agency for Research on Cancer. WHO classification of tumours editorial board. Digestive system tumours, 5th edition WHO classification of tumours series. Lyon: International Agency for Research on Cancer; 2019.
[3] International Agency for Research on Cancer. WHO classification of tumours editorial board. Paediatric tumours, 5th edition WHO classification of tumours series. Lyon: International Agency for Research on Cancer; 2022.
[4] ISSVA Classification & Glossary for Vascular anomalies by international Society for the Study of Vascular anomalies. 2025 [owned by ISSVA].
[5] MacSween's Pathology of the liver. 8. Edition 2024. p. 902 [subchapter infantile haemangioma].
[6] Triana P, Rodríguez-Laguna L, Giacaman A, et al. Congenital hepatic hemangiomas: clinical, histologic, and genetic correlation. J Pediatr Surg 2020;55:2170–6.
[7] Ayturk UM, Couto JA, Hann S, et al. Somatic activating mutations in GNAQ and GNA11 are associated with congenital hemangioma. Am J Hum Genet 2016 Apr 7;98(4):789–95. Erratum in: Am J Hum Genet. 2016 Jun 2;98-(6):1271.
[8] Berenguer B, Mulliken JB, Enjolras O, et al. Rapidly involuting congenital hemangioma: clinical and histopathologic features. Pediatr Dev Pathol 2003 Nov-Dec;6(6):495–510.
[9] Ugwu N, Atzmony L, Ellis KT, et al. Cutaneous and hepatic vascular lesions due to a recurrent somatic *GJA4* mutation reveal a pathway for vascular malformation. HGG Adv 2021 Apr 8;2(2):100028.
[10] Funk T, Lim Y, Kulungowski AM, et al. Symptomatic congenital hemangioma and congenital hemangiomatosis associated with a somatic activating mutation in *GNA11*. JAMA Dermatol 2016;152(9):1015–20.
[11] North PE, Waner M, Mizeracki A, Mihm Jr MC. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol 2000 Jan;31(1):11–22.
[12] Léauté-Labrèze C, Harper JI, Hoeger PH. Infantile haemangioma. Lancet 2017 Jul 1;390:85–94. 10089.
[13] Jinnin M, Medici D, Park L, Limaye N, et al. Suppressed NFAT-dependent VEGFR1 expression and constitutive VEGFR2 signaling in infantile hemangioma. Nat Med 2008;14:1236–46.
[14] Gill RM, Buelow B, Mather C, et al. Hepatic small vessel neoplasm, a rare infiltrative vascular neoplasm of uncertain malignant potential. Hum Pathol 2016 Aug;54:143–51.
[15] Joseph NM, Brunt EM, Marginean C, et al. Frequent GNAQ and GNA14 mutations in hepatic small vessel neoplasm. Am J Surg Pathol 2018 Sep;42(9):1201–7.
[16] [a] Mulholland P, Goh IY, Sokolova A, Liu C, Siriwardhane M. Hepatic small vessel neoplasm case report: a surveillance conundrum. Int J Surg Case Rep 2021 Apr;81:105742.[b] McAllister KA, Grogg KM, Johnson DW, et al. Endoglin, a TGF-β binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Nat Genetics 1994 Dec;8(4):345–51.
[17] Akanuma N, Joseph NM, Stachler M, Behr S, Takahashi T, Gill RM. Malignant hepatic vascular neoplasm with novel RAF1 and GNA11 mutations: risk stratification considerations for hepatic small vessel neoplasm (HSVN). Hum Pathol Rep 2022;29:300671.
[18] Berg JN, Gallione CJ, Stenzel TT, et al. The activin receptor-like kinase 1 gene: genomic structure and mutations in hereditary hemorrhagic telangiectasia type 2. Am J Hum Genet 1997 Jul;61(1):60–7.
[19] Gallione CJ, Repetto GM, Legius E, et al. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). Lancet 2004 Mar 13;363(9412):852–9.
[20] Johnson DW, Berg JN, Baldwin MA, et al. Mutations in the activin receptor–like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. Nature 1996 Jun;3(2):189–95.
[21] McAllister KA, Baldwin MA, Thukkani AK, et al. Six novel mutations in the endoglin gene in hereditary hemorrhagic telangiectasia type 1 suggest a dominant-negative effect of receptor function. Hum Mol Genet 1995 Oct;4(10):1983–5.
[22] Fischer AK, Beckurts KTE, Büttner R, Drebber U. Giant cavernous hemangioma of the liver with satellite nodules: aspects on tumour/tissue interface: a case report. World J Hepatol 2023 May 27;15(5):707–14. https://doi.org/10.4254/wjh.v15.i5.707. PMID: 37305366; PMCID: PMC10251275.
[23] Italiano A, Chen CL, Thomas R, et al. Alterations of the p53 and PIK3CA/AKT/mTOR pathways in angiosarcomas: a pattern distinct from other sarcomas with complex genomics. Cancer 2012 Dec 1;118(23):5878–87. https://doi.org/10.1002/cncr.27614.
[24] Hubbard KB, Hepler JR. Cell signalling diversity of the Gq-alpha family of heterotrimeric G proteins. Cell Signal 2006;18:135–50.
[25] Schrenk S, Bischoff LJ, Goines J, et al. MEK inhibition reduced vascular tumour growth and coagulopathy in a mouse model with hyperactive GNAQ. Nat Commun 2023;14:1929.

[26] Nguyen HL, Boon LM, Vikkula M. Trametinib as a promising therapeutic option in alleviating vascular defects in an endothelial KRAS-induced mouse model. Hum Mol Genet 2022 Jan 6;32(2):276–89. https://doi.org/10.1093/hmg/ddac169.
[27] Lim YH, Bacchiocchi A, Jingyao Q, et al. GNA14 Somatic mutation causes congenital and sporadic vascular tumours by MAPK activation. Am J Hum Genet 2016;99:443–50.
[28] Shirley MD, Hao Tang, Gallione C, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. N Engl J Med 2013;368:1971–9.
[29] Menke J, Schaefer IM. A large liver tumour in a 3-month-old girl. Diagnosis: GLUT1-negative hepatic vascular malformation with capillary proliferation. Gastroenterology 2011 Jun;140(7):1883–2151. https://doi.org/10.1053/j.gastro.2010.12.042.