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Papillary Hemangioma Harbors Somatic *GNA11* and *GNAQ* mutations

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Abstract

Papillary hemangioma (PH) is a small, primarily dermal lesion occurring predominantly in the head and neck in both children and adults. Its signature characteristics are dilated thin-walled channels containing papillary clusters of mainly capillary-sized vessels and endothelial cytoplasmic eosinophilic inclusions. Given certain histopathologic similarities to congenital hemangioma which harbor mutations in *GNAQ* and *GNA11*, we investigated whether similar mutations are present in PH. Seven PH specimens were studied. All presented in first four years of life, with one being noted at birth. With the exception of one lesion, all were in the head and neck. Lesions were bluish and ranged in size from 0.5 to 2.8 cm. Four samples had *GNA11* p.Q209L and three had *GNAQ* p.Q209L missense mutations. Mutations in *GNA11* and *GNAQ* are associated with other types of somatic vascular lesions including capillary malformation, congenital hemangioma, anastomosing hemangioma, thrombotic anastomosing hemangioma, and hepatic small cell neoplasm. Shared mutations in *GNA11* and *GNAQ* may account for some overlapping clinical and pathologic features in these entities, perhaps explicable by the timing of the mutation or influence of the germline phenotype.

Keywords

hemangioma; GNA11; mutation; papillary; vascular; GNAQ

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Introduction

Papillary hemangioma (PH) is an uncommon lesion originally described in 2007 by Suurmeijer and Fletcher (1). Their cohort consisted of 11 patients, with an age range of 2 to 77 years (median of 57), with 3 being in the pediatric age group. It manifests as a small bluish cutaneous papule occurring primarily in the head and neck region (1). The dermal lesion is typically composed of dilated, thin-walled channels with papillary clusters of mainly capillary-sized vessels and endothelial cytoplasmic hyaline globules. Since their initial cohort of 11 patients, a limited number of case reports have identified few additional cases (2–4), presently, molecular alterations in PH have not been identified. These lesions follow a benign clinical course and treatment is complete excision; however, one patient in the original study presented 10 years after initial diagnosis with a recurrent lesion.

Papillary hemangiomas share several clinical and histologic similarities with other vascular anomalies such as non-involuting congenital hemangioma (5), and anastomosing hemangioma. These other vascular anomalies harbor mutations within *GNAQ*, and *GNA11*(6–9). Therefore, we decided to investigate whether PH harbors the same mutations.

Materials & Methods

The Committee on Clinical Investigation at Boston Children's Hospital and Nationwide Children's Hospital approved this study. An archival search yielded seven cases of papillary hemangioma. Clinical data and histopathology were reviewed, and DNA was extracted from available formalin-fixed paraffin-embedded tissue samples and subjected to molecular analysis.

Droplet digital PCR (ddPCR) (cases 1–5 and 7)

We developed droplet digital PCR (ddPCR) assays for the known *GNA11* (c.626A>T;p.Q209L) and *GNAQ* (c.626A>T;Q209L) mutations identified in congenital hemangioma(10). For each mutation, DNA primers and Taq-man fluorescent probes specific for either the wild-type or mutant allele were developed (Integrated DNA Technologies). Genomic DNA was extracted from each sample using the DNeasy Blood & Tissue kit (Qiagen). Approximately 30 nanograms of template genomic DNA were used in each reaction. The reaction mixture was partitioned into ~20,000 droplets using the QX200 Droplet Generator (Bio-Rad), subjected to 40 PCR cycles, and then analyzed using the QX200 Droplet Reader and QuantaSoft software (both from Bio-Rad). Each reaction was carried out in at least a technical triplicate and mutant allele frequency was determined based on the average droplet counts in each reaction. Other vascular anomalies without either the *GNA11* p.Q209L and *GNAQ* p.Q209L mutations were utilized in our assay as negative controls.

Paired Exome Sequencing (Patient 6)

Paired somatic disease-germline comparator exome sequencing was performed under a Nationwide Children's Hospital IRB-approved protocol for patients with suspected somatic disease (IRB17–00206). Peripheral blood served as the source of the germline comparator,

with FFPE tissue from an excisional biopsy of the left arm. Libraries were prepared using 100 ng and 500 ng of input DNA (derived from blood and FFPE, respectively), beginning with enzymatic fragmentation, followed by end repair, 5' phosphorylation, A-tailing, and adapter ligation using NEB Ultra II FS (New England Biolabs, Ipswich, MA). Enrichment of targeted regions by hybridization capture was performed with IDT xGen Lockdown v2.0 human exome reagent enhanced with the xGenCNV Backbone Panel and Cancer spike-in (Integrated DNA Technologies, Coralville, IA). Paired-end 151-bp reads were generated on the Illumina NovaSeq (Illumina, Inc., San Diego, CA). Secondary analysis was performed using Churchill, a comprehensive workflow for taking raw reads from alignment through to germline and somatic variants calls (11). Each sample was sequenced to high-depth achieving >100X average read coverage (166X blood; 102X FFPE tissue). Somatic single nucleotide variation (SNV) and insertion-deletion detection was performed using GATK's MuTect-2 (12).

Results

Clinical features

The age at presentation ranged from birth to four years and four patients were female. All but one lesion was located on the head and neck as one patient had a PH on his arm. (Table 1). They were clinically described as bluish papules ranging in size from 0.5 to 2.8 cm at time of diagnosis. The lesions slowly increased in size with age (Figure 1). All were excised between 3 and 8 years of age. There were no significant differences in age at presentation, sex, or presenting symptom nor in PH location, size, or histopathologic appearance. Additionally, there were no phenotypic differences between patients with *GNA11* or *GNAQ* mutations.

Pathologic features

Morphologically, all lesions were centered in the dermis with variable extension into the subcutaneous tissue (Figure 2). Round-to-ovoid ectatic, thin-walled blood vessels with little or no smooth muscle, anchored polypoid and papillary vascular fronds that occupied their lumens to a varying degree (Figures 2, 3, 4). The sparse stroma of the fronds had mostly capillary-type channels although their caliber was often considerably greater. Cytoplasmic eosinophilic hyaline globules were present within some endothelial cells within the fronds (Figure 3, 4). Also seen were strands of hyalinized stroma (Figure 3) and mostly non-organizing fibrin-rich thrombi (Figure 4).

Genomic findings

All 7 lesions were found to have mutations in either *GNA11* or *GNAQ*. Of the 6 where ddPCR was successfully able to identify a mutation, 4 had a *GNA11* p.Q209L (c.626A>T) mutation and 2 had a *GNAQ* p.Q209L (c.626A>T) mutation. The variant allele frequencies (VAF) ranged from 7.92% to 10.72% (Table 1). One (case 6) was analyzed using paired exome sequencing of both the lesion and blood, which identified a somatic *GNAQ* p.Q209L (c.626A>T) mutation.

Discussion

In this study, we identified somatic mutations in *GNA11* and *GNAQ* at the codon 209 hotspot in papillary hemangiomas (PH), further expanding the spectrum of vascular anomalies with *GNA11* and *GNAQ* mutations. This will help in identification of PH and to distinguish it from its mimickers. Of note, there was no specific genotype-phenotype correlation in the PHs that had mutations in *GNAQ* compared to those with mutations in *GNA11*. Mutations in *GNAQ* and *GNA11* were first identified in uveal melanoma at 2 recurrent hotspots (R183 in exon 4 and Q209 in exon 5). Since, mutations 1 or more members (*GNAQ*, *GNA11*, and *GNA14*) of the GNA (G protein subunits alpha) family have been reported in several vascular anomalies, including rapidly involuting congenital hemangioma(13), noninvoluting congenital hemangioma (5) (5, 13), anastomosing hemangioma (7), thrombotic anastomosing hemangioma (9), hepatic small vessel neoplasm (8), Campbell De Morgan spot (14), and the capillary malformation in Sturge-Weber syndrome (15) (Table 2).

GNA11 and *GNA14* are considered paralogs of *GNAQ* since they share approximately 90% and 80% of their amino acid sequence, respectively (8). This leads to similar structure and function of their encoded proteins. These belong to a family of guanine nucleotide-binding proteins (G proteins) that form the trimeric G protein complex that binds to a G protein coupled receptor, activating a variety of downstream pathways involved in cell growth, differentiation and survival. Mutations at the R183 and Q209 hotspots in *GNAQ* and *GNA11* result in constitutive activation of the G-protein and increased downstream signaling through the MAPK pathway. The variant allele frequency (VAF) was low in all of the cases. This is expected, as vascular anomalies often only have a small proportion of endothelial cells harboring the mutation present in the sample. There is a variety of other cell types present, which lowers the expected VAF. These include normal vessels, inflammatory cells, and stromal cells, among others. This highlights the importance of having a very sensitive assay when performing sequencing on vascular anomalies. Microdissection to enrich for the lesional areas can be helpful.

In the differential diagnosis of PH in the pediatric setting, congenital hemangioma, specifically NICH, is the lesion most likely to be considered. PH is not usually noted at birth and presents as a flat-to-slightly raised, bluish, small papule whereas NICH is, by definition congenital, as well as larger, raised or plaque-like, pink- to-purple, and often has coarse telangiectasia and a pale halo (16). NICH is also comprised of variably-sized lobules of small, thin-walled vessels and many lesions contain thrombi and eosinophilic hyaline cytoplasmic globules. Occasional NICHs also focally have a “pseudo-papillary” appearance. The interlobular stroma in NICH is often enriched for dilated, dysmorphic veins which is a helpful distinguishing feature.

Other lesions such as infantile hemangioma, tufted angioma (TA), kaposiform hemangioendothelioma (KHE), Kaposi sarcoma, and glomeruloid hemangioma have certain histopathologic features in common with PH but clinical, radiographic, histopathologic, and molecular findings all contribute to the appropriate diagnosis (3, 17–20). For example, infantile hemangiomas typically arise in the newborn period and then undergo a proliferative

phase followed by involution over several years. This is in contrast to our cases of PH, some of which increased in size over time. Infantile hemangiomas also express GLUT-1. Tufted angioma and KHE are likely related biologically, as both can harbor *GNA14* mutations, are morphologically similar, and cause Kasabach-Merritt phenomenon. TA is comprised of well-circumscribed vascular tufts in a “cannonball” pattern located in the dermis. KHE is morphologically similar, but with additional larger, less well-defined nodules with spindled endothelial cells that form thin, slit-like lumina. Both TA and KHE expresses lymphatic markers such as D240 or PROX1. Kaposi sarcoma is often comprised of spindle cells that form slit-like vessels with increased mitotic activity and is associated with HHV8 infection. These can behave aggressively and develop visceral dissemination, unlike PH. Glomeruloid hemangioma is formed by capillary-type vasculature that forms glomeruloid structures and can have PAS+ cytoplasmic globules similar to PH. However, these are associated with Castleman disease and POEMS syndrome.

In sum, the data in this study suggests that PH shares molecular biology with several other vascular anomalies. This raises the question of whether or not these anomalies represent distinct entities or if they are all part of the same spectrum. Even though these anomalies have similar, or in certain instances, identical mutations, their clinical and histopathological features are distinctly different. Some possible factors accounting for these differences include the patient’s germline phenotype, the time of occurrence of the mutation, and epigenetic or environmental factors. Further, our identification of *GNAQ* and *GNA11* mutations in PH will aid in its diagnosis and help to differentiate it from other vascular anomalies that lack these mutations.

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References:

1. Suurmeijer AJ, Fletcher CD. Papillary haemangioma. A distinctive cutaneous haemangioma of the head and neck area containing eosinophilic hyaline globules. Histopathology. 2007;51(5):638–48. [PubMed: 17927585]
2. Bancalari B, Colmenero I, Noguera-Morel L, et al. Papillary hemangioma in a child and sonographic characterization. Pediatr Dermatol. 2020;37:233–4. [PubMed: 31782833]
3. Maloney N, Miller P, Linos K. Papillary Hemangioma: An Under-Recognized Entity Not to Be Confused With Glomeruloid Hemangioma. Am J Dermatopathol. 2020;42(3):211–4. [PubMed: 31592865]
4. Geetha SD, Abdelwahed M, Edelman MC, et al. A Rare Case of Intraosseous Papillary Hemangioma of the Head and Neck. International journal of surgical pathology. 2023.
5. Ellison DW, Dalton J, Kocak M, et al. Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. Acta neuropathologica. 2011;121(3):381–96. [PubMed: 21267586]
6. Ayturk UM, Couto JM, Hann S, et al. Somatic Activating Mutations in GNAQ and GNA11 Are Associated with Congenital Hemangioma. Am J Hum Genet. 2016;98(4):789–95. [PubMed: 27058448]
7. Bean GR, Joseph NM, Gill RM, et al. Recurrent GNAQ mutations in anastomosing hemangiomas. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2017;30:722–7. [PubMed: 28084343]

8. Joseph NM, Brut EM, Marginean C, et al. Frequent GNAQ and GNA14 Mutations in Hepatic Small Vessel Neoplasm. The American journal of surgical pathology. 2018;42:1201–7. [PubMed: 29975248]

9. Liau JY, Lee J, Tsai JH, et al. Thrombotic Hemangioma With Organizing/Anastomosing Features: Expanding the Spectrum of GNA-mutated Hemangiomas With a Predilection for the Skin of the Lower Abdominal Regions. The American journal of surgical pathology. 2020;44:255–62. [PubMed: 31633489]

10. Hindson BJ, Ness KD, Masquelier DA et al. High-throughput droplet digital PCR system for absolute quantitation of DNA copy number. Anal Chem. 2011;83(22):8604–10. [PubMed: 22035192]

11. Kelly BJ, Fitch JR, Hu Y et al. Churchill: an ultra-fast, deterministic, highly scalable and balanced parallelization strategy for the discovery of human genetic variation in clinical and population-scale genomics. Genome Biol. 2015;16(1):6. [PubMed: 25600152]

12. Cibulskis K, Lawrence MS, Carter SL et al. ensitive detection of somatic point mutations in impure and heterogeneous cancer samples. Biotechnol. 2013;31(3):213–9.

13. Hawkes J, Campbell J, Garvin D, et al. Lack of GNAQ and GNA11 Germ-Line Mutations in Familial Melanoma Pedigrees with Uveal Melanoma or Blue Nevi. Front Oncol. 2013;3.

14. Liau JY, Lee J, Tsai JH, et al. High frequency of GNA14, GNAQ, and GNA11 mutations in cherry hemangioma: a histopathological and molecular study of 85 cases indicating GNA14 as the most commonly mutated gene in vascular neoplasms. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2019;32:1657–65. [PubMed: 31189994]

15. Pinto A, Sahin M, Pearl PL. Epileptogenesis in neurocutaneous disorders with focus in Sturge Weber syndrome. F1000Res. 2016;18(F1000 Faculty Rev-370).

16. Enjolras O, Mulliken JB, Boon LM, et al. Noninvoluting congenital hemangioma: a rare cutaneous vascular anomaly. Plast Reconstr Surg. 2001;107:1647–54. [PubMed: 11391180]

17. Wassef M, Blei F, Adams D, et al. Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies. Pediatrics. 2015;136:e203–14. [PubMed: 26055853]

18. Gupta A, Kozakewich HW. Histopathology of vascular anomalies. Clin Plast Surg. 2011;38:31–44. [PubMed: 21095470]

19. Sadick M, Muller-Wille R, Wildgruber M, et al. Vascular Anomalies (Part I): Classification and Diagnostics of Vascular Anomalies. Rofo. 2018;190:825–35. [PubMed: 29874693]

20. Nguyen HL, Boon LM Vikkula M. Genetics of vascular anomalies. Semin Pediatr Surg. 2020;29:150967. [PubMed: 33069286]

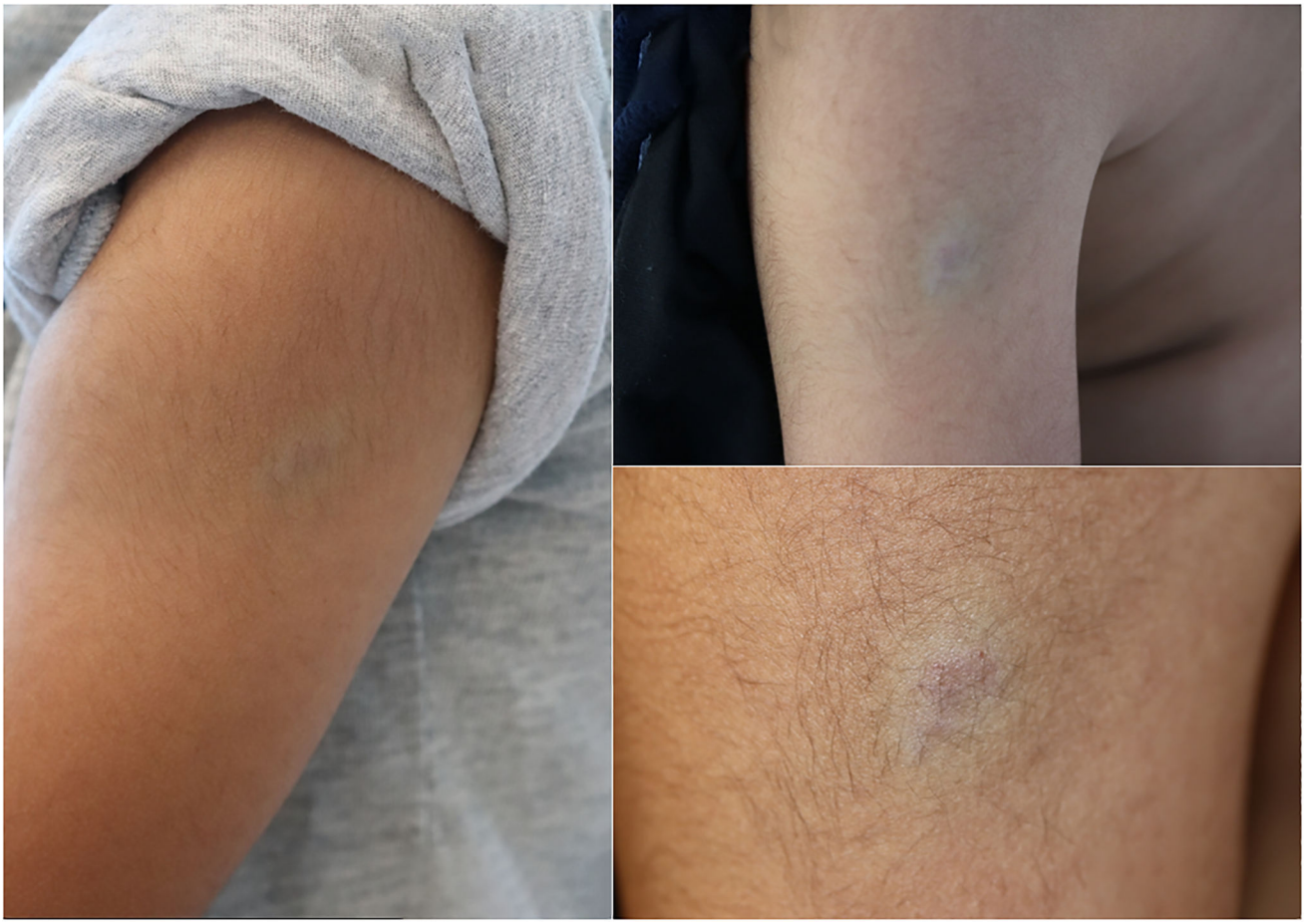

Figure 1.

A) Patient 6, a 7-year-old male with a slightly raised blue-to-purple arm lesion with a pale blue-to-white surrounding halo. B,C) Lesion remaining stable over approximately 19 months later.

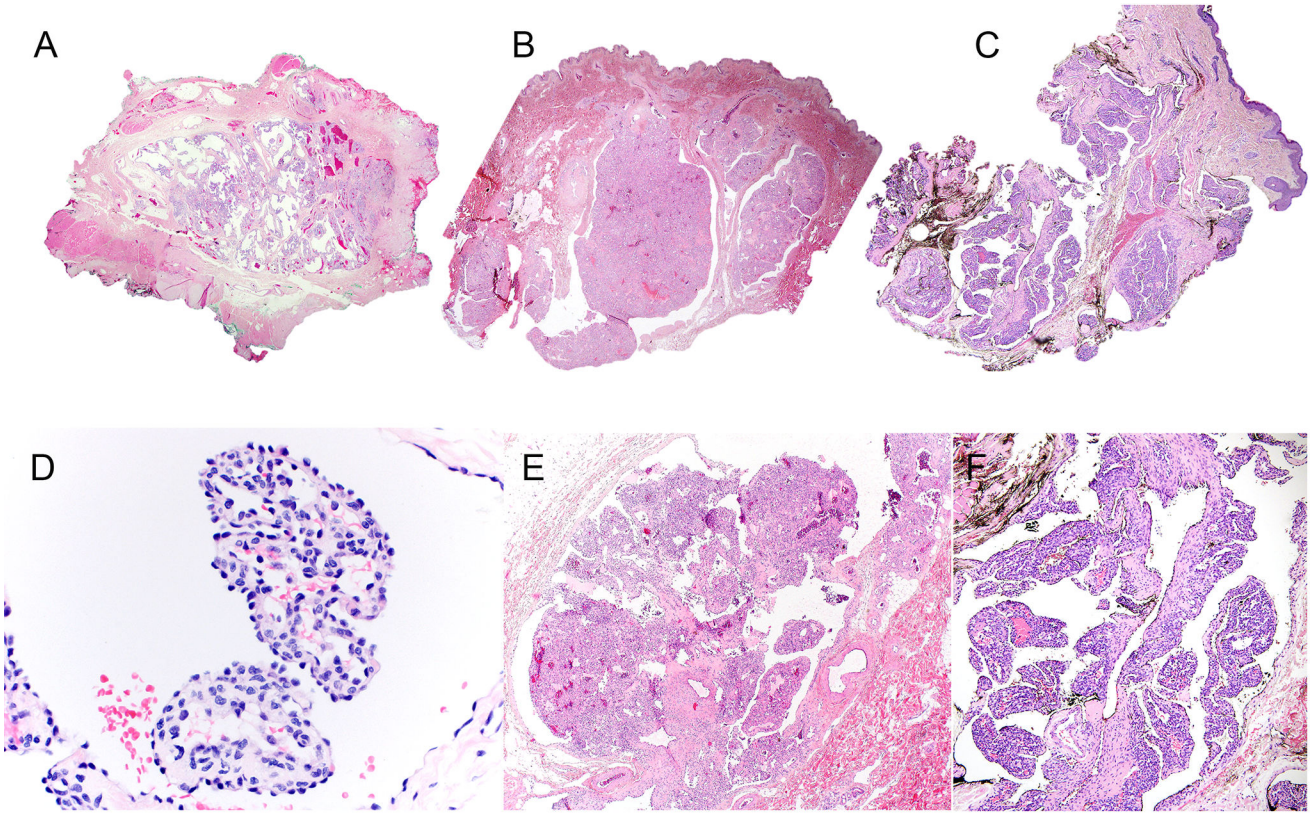

Figure 2.

A-C) Lesions located within dermis with variable subcutaneous extension. A. Case 2 with dilated vessels. B. Case 1 being more solid-appearing with closely approximated channels. C. Case 6 with classic papillary pattern. D-F. Thin-walled vessels with polypoid-to-papillary fronds.

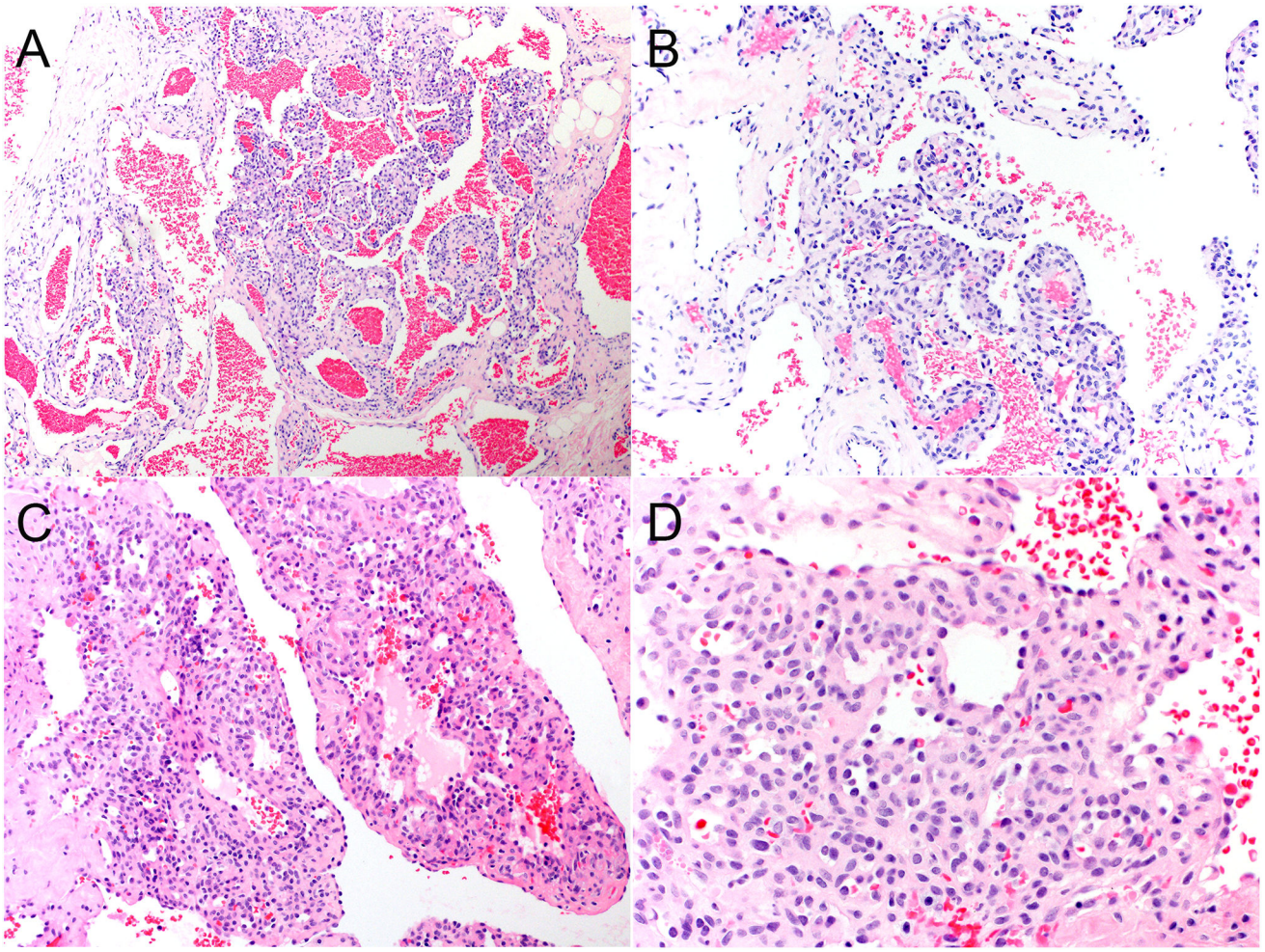

Figure 3.

A.B.C. Foci of hyalinized stroma. D. Plump endothelial cells, some containing cytoplasmic eosinophilic hyaline globules.

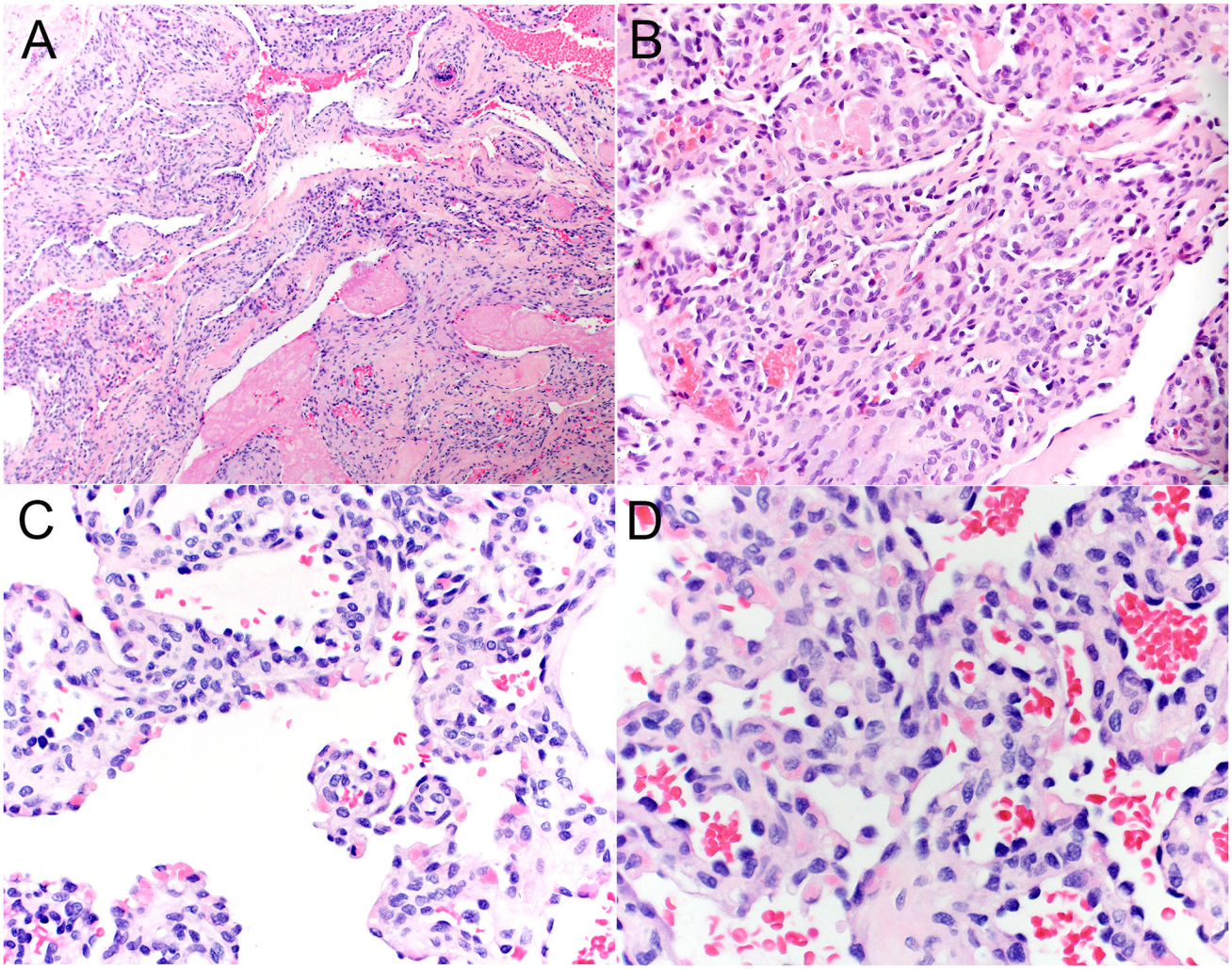

Figure 4.

A.B. Organizing fibrin-rich thrombi. C.D. Plump endothelial cells containing eosinophilic hyaline globules.

Table 1.

Patient characteristics and corresponding somatic mutation.

Patient	Sex	Age at presentation (years)	Age at excision (years)	Location	Size (cm)	Mutation (VAF %)
1	M	Birth	8	Neck	2.5	*GNA11* c.626A>T p.Q209L (8.73%)
2	F	1	3	Post-auricular	≤ 1.8	*GNA11* c.626A>T p.Q209L (10.72%)
3	M	2	3.5	Lip	0.6	*GNA11* c.626A>T p.Q209L (7.92%)
4	F	Unknown	4	Post auricular	2.1	*GNAQ* c.626A>T p.Q209L (10.32%)
5	F	3	4	Lip	0.5	*GNA11* c.626A>T p.Q209L (9.93%)
6	M	3	7	Arm	1.2	*GNAQ* c.626A>T p.Q209L (8.43%) *
7	F	4	12	Scalp	2.8	*GNAQ* c.626A>T p.Q209L (10.43%)

M: Male, F: Female, VAF: variant allele frequency

* **Transcript Designation:** NM_002072.5(*GNAQ*); NM_002067.5(*GNA11*) (Detected by NGS exome sequencing)

Table 2.

Vascular anomalies harboring *GNAQ*, *GNA11*, or *GNA14* mutations.

Vascular anomaly	**Mutations**
Papillary hemangioma	*GNAQ*, *GNA11* at codon 209
Congenital hemangioma	*GNAQ*, *GNA11* at codon 209
Capillary malformation (Sturge-Weber Syndrome)	*GNAQ*, *GNA11* at codon 183
Anastomosing hemangioma	*GNAQ* at codon 209
Thrombotic anastomosing hemangioma	*GNAQ*, *GNA11*, and *GNA14* at codons 205, 209
Hepatic small vessel neoplasm	*GNAQ*, *GNA14* at codons 48, 205, 209; rare *PIK3CA*
Campbell De Morgan spot (senile hemangioma or cherry angioma)	*GNAQ*, *GNA11*, and *GNA14* at codons 205, 209
Tufting angioma/Kaposiform hemangioendothelioma	*GNA14* at codon 205