Congenital hemangiomas and infantile hemangioma: Missing links

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Rapid postnatal growth and slow involution in childhood characterize the common infantile hemangioma. There are other rare vascular tumors that present fully grown at birth and behave quite differently, as designated by the acronyms: rapidly involuting congenital hemangioma (RICH) and noninvoluting congenital hemangioma (NICH). RICH and NICH have similarities in appearance, location, size, equal sex ratio, and both have overlapping radiologic and histologic features with infantile hemangioma. However, neither type of congenital tumor immunostains for glucose transporter-1 protein, a marker of infantile hemangioma. This raises the question of whether these congenital vascular lesions are variations in a spectrum of hemangioma or are entirely different tumors. We describe two groups of patients that suggest a linkage between postnatal and congenital vascular tumors: Link I (n=5), children who had either RICH or NICH coexisting with infantile hemangioma, and Link II (n=10), children initially diagnosed as having RICH, but regression was incomplete and the residuum was that of NICH. We conclude that these infants exhibit "missing links" between the rare RICH and NICH, and the common infantile hemangioma. (J Am Acad Dermatol 2004;50:875-82.)

The typical infantile hemangioma (IH) appears postnatally, grows rapidly, and regresses slowly. About one third of IHs are nascent at birth; the majority appear around 2 weeks, although deep-seated tumors may not be noticed until 2 to 4 months of life. The term *congenital hemangioma* was introduced to denote a vascular tumor that had grown to its maximum size at birth and does not exhibit accelerated postnatal growth.[1]

Congenital hemangiomas do not look like the precursor (nascent) lesions of IH, and they behave quite differently from IH as well. There are at least two major subgroups: *rapidly involuting congenital hemangioma* (RICH)[2] and *noninvoluting congenital hemangioma* (NICH).[3] The dissimilar growth patterns of the two forms of congenital hemangioma (RICH and NICH) and IH are illustrated in Fig 1. The RICH curve has the same configuration as that of IH, but as regression progresses rapidly during the first year, the curve is compressed along the y-axis and shifted to the left. The NICH curve remains flat following birth and into childhood. It is as if NICH is caught in a persistently fast-flow state, unable to undergo postnatal regression. Curiously, RICH leaves behind a residual patch of thin skin with prominent veins and little, if any, subcutaneous fat. This is in remarkable contrast to the slowly regressing IH that sometimes transforms into a fatty lesion by the involuted phase. We have no explanation for the equal sex distribution in the two types of congenital hemangioma,[1,3] which contrasts with the well-known female preponderance in IH.

The microscopic findings in NICH[3] have been compared to those in RICH and to common infantile hemangioma.[2] In general, although the histologic characteristics differ among these three types of tumors, there are some overlapping features as well. North and colleagues[4] discovered that the endothelium in infantile hemangioma immunostains for glucose transporter-1 protein (GLUT1) throughout the tumor's life cycle. However, other vascular tumors are immunonegative, and these authors have suggested that GLUT1 is a specific marker for infantile hemangioma.[5] However, neither RICH (with rare exceptions) nor NICH stains with GLUT1 antibodies.[2,3] These observations raise the question of whether the two types of congenital hemangioma, RICH and NICH, are related to infantile hemangioma *or are they distinct tumors.* Furthermore, what is the connection, if any, between RICH and NICH, both

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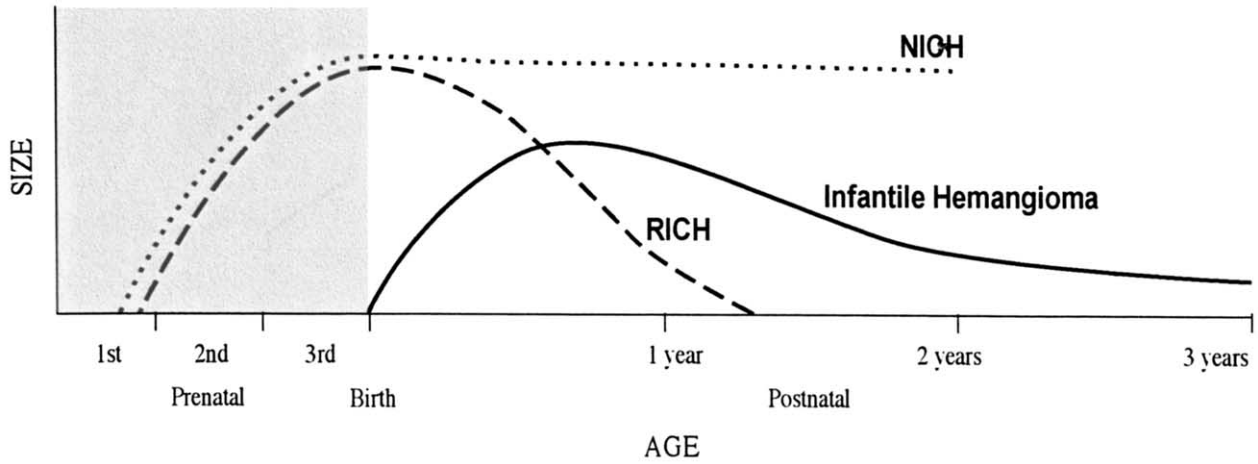

Fig 1. Growth curves for rapidly involuting hemangioma (RICH), non-involuting hemangioma (NICH) and infantile hemangioma (IH).

tumors of prenatal onset that exhibit such divergent postnatal behavior?

We describe two groups of children with vascular tumors that suggest possible answers to these questions. We call these patients the "missing links," in an analogous sense to the discovery of hypothetical intermediate forms between modern man and his prehistoric progenitors. There are two group of linking patients: Link I, infants who have a RICH or a NICH in addition to a common postnatal infantile hemangioma (n=5), and Link II, infants who have a large congenital vascular tumor that initially looked like RICH and began to regress rapidily, but later ceased to involute, resulting in a residual fast-flow tumor that is typical of NICH (n=10).

CASE REPORTS

Link I: coexistence of congenital vascular tumor (NICH or RICH) and infantile hemangioma

The clinical characteristics of the 5 patients in this group are summarized in Table I. There were 3 girls and 2 boys. Four were full-term, and one (patient 5) was born at 39 weeks. The location of the congenital tumors was equally distributed over the body: 1 was a RICH and 4 were NICH, the latter determined by appearance and unchanged fast-flow (Figs 2 and 3). The typical infantile hemangiomas appeared after birth; only one was located close to the congenital tumor (patient 3).

Link II: transformation from RICH to NICH

The findings in these 10 patients are shown in Table II. All were healthy, full-term infants; there were 8 boys and 2 girls. The congenital tumor seemed to have a predilection for the lower extremity. All tumors had a similar appearance at birth, that is, telangiectatic, purple, and bossed, and all involuted rapidly during the first year of life, fulfilling the criteria for RICH. However, these lesions failed to regress completely and remained with the clinical features of NICH (Figs 4-6). Persistent fast-flow, characteristic of NICH, was noted in 6 patients; Doppler examination was not done in the other 4 patients. Resection was necessary in 5 patients because of the tumor's appearance or pain, and the histologic findings were those of NICH rather than RICH.

DISCUSSION

Hemangioma occurs in 4% to 10% of white infants.[6] The typical appearance, variable morphology, and natural evolution are well known. About one third of these tumors appear with premonitory neonatal signs, usually a red macule, blanched spot, pseudoecchymotic stain, or localized telangiectasia.[7,8] More commonly, cutaneous hemangiomas manifest at a median age of 2 weeks. There is rapid growth during the first year of life (proliferating phase), slow regression from 1 to 7 years (involuting phase), and complete regression after 8 year of age (involuted phase).[9,10]

"Treasure your exceptions" said Bateson, for they tell you there is more to learn and suggest where to direct your next inquiry.[11] Indeed, there are exceptional vascular tumors that look rather like infantile hemangioma, but they exhibit a different scenario. Bowers and colleagues,[12] in their study of the life cycle of hemangioma, noted a curious case of a large "strawberry nevus" on the posterior thorax that resolved spontaneously by 16 weeks. Two similar examples are illustrated in the 1988 textbook by Mul-

Table I. Link I: Coexistence of *c*ongenital *v*ascular *t*umor and *i*nfantile *h*emangioma

Patient No.	Sex	Congenital vascular tumor (location)	Infantile hemangioma (time of appearance)	Course	Associated findings
1	F	Raised, violaceous, telangiectatic; pale rim, (thigh) U/S fast-flow (2 y) = NICH	Supraorbital, deep (2 mo)	NICH unchanged @ 2 y IH involuting	VSD, anal ectopia, microcephaly, seizures, developmental delay
2	F	Pale bluish slightly elevated (chest). U/S fast-flow (5 y) = NICH	Upper labial (2 wk)	NICH stable. IH treated with steroid & excised (GLUT1+)	None
3	M	Large (6cm) flat pink, hemispheric, telangiectatic, (upper thigh) = NICH	Ipsilateral thigh (2 wk)	NICH stable. IH involuting @ 18 mo	None
4	M	Large, (7×4cm), ovoid, pale rim, coarse telangiectasia (arm) = NICH	Frontal, superficial & deep (1 mo)	NICH stable. IH involuting @ 1 y	Growth/mental retardation, microcephaly, strabismus
5	F	Violaceous large mass, central telangiectasia (nape) = RICH	Abdominal, superficial (1 wk)	RICH involuting IH growing @ 3.5 mo	None

F, Female; *GLUT1*, glucose transporter-1 protein; *IH*, infantile hemangioma; *M*, male; *NICH*, noninvoluting congenital hemangioma; *RICH*, rapidly involuting congenital hemangioma; *U/S*, ultrasonography; *VSD*, ventricular septal defect.

liken and Young,[9] but the significance of this unusual behavior was underappreciated. In their paper entitled "Not All Hemangiomas Look Like Strawberries," Martínez-Pérez and coworkers commented on 5 curious tumors, all located in an extremity that were fully grown at birth and involuted rapidly.[13] They called this variant "bossed hemangioma with telangiectasia and peripheral pallor." One year later, the vascular anomalies teams in Boston and Paris designated the identical lesion *congenital hemangioma* and presented 31 examples.[1]

These congenital vascular tumors have a slightly variable morphology; however, common features include violaceous color with multiple tiny or coarse telangiectasias, often a surrounding pale halo, and sometimes a central ulceration, linear scar, or central nodularity. All tumors initially exhibit fast-flow by ultrasonography and magnetic resonance imaging (MRI).[1] Their defining feature is accelerated regression by 12-14 months of age, leaving behind expanded or slightly depressed, atrophic skin with normal blood flow. The sonographic,[14] magnetic resonance and angiographic[15] appearance of this type of congenital hemangioma differs slightly from that of infantile hemangioma. Six similar tumors were called "congenital nonprogressive hemangioma" by North and colleagues[16] in a study that focussed on histologic findings. However, resection was carried out very early in these infants, between 9 and 2.5 months of age, so the natural history of their lesions is unknown.

Since a congenital hemangioma is fully grown at birth, it must have arisen in utero. Indeed, this type of vascular tumor has been detected by antenatal ultrasonography, as early as the end of the first trimester[1] and, more commonly, at the beginning of the second trimester.[17,18] Most prenatally discovered lesions have been a single large tumor of the scalp or neck, and, less frequently, in an extremity, the other typical location for the congenital tumors.[2] Ultrasonographically observed lesions either have exhibited rapid postnatal regression[17,19-22] or were excised in infancy.[23,24] In two instances, the neonate died of complications of the tumor.[25,26] There are also examples of antenatal diagnosis of single and multiple intrahepatic hemangiomas,[27-29] and two case reports of prenatal treatment of the fetus, via the mother, either with corticosteroid[30,31] or interferon.[32]

Table II. Link II: Transformation of RICH to NICH

Patient No.	Sex	Congenital *V*ascular *T*umor (location)	Outcome	Investigation
6	M	Ovoid bossed, central pallor and telangiectasia, 4 cm (leg) = RICH	Regression over 1 y, leaving depressed pink area with pale rim; resected at 4.5 y	U/S fast-flow. *H*istology = NICH
7	F	Round, violaceous telangiectatic, 6 cm (temple) = RICH	Regression (75%) ceased at 1 y. Residuum @ 2 y (slightly elevated, coarse telangiectasia, pallor) = NICH.	None
8	M	Bossed, pink telangiectatic, 6 cm (ankle) = RICH	Rapid regression ceased at 4 mo, leaving residual ovoid, pink lesion with pale rim = NICH. No further regression @ 17 mo.	None
9	M	Well-demarcated, elevated, violaceous center, pale rim, 9×3 cm (abdomen) = RICH	Regressed for 9 mo. and remained stable at 2.5 years = NICH.	U/S fast-flow
10	M	Bossed, coarse telangiectasia, central white scar, thin pale rim, 7 cm (thigh) = RICH	Rapid involution ceased at 8 mos, leaving telangiectatic pink plaque, central scar, thin pale halo. Proportionate growth 8-11 yrs. with prominent veins. (17 cm diam.) = NICH. Resected @ 11 y	U/S fast-flow. Histology = NICH
11	M	Ovoid, bossed, 3 cm (abdomen) = RICH	Rapid regression for 1 y, residuum flat, pale halo = NICH. Resected for increasing pain and large draining veins @ 4 y	U/S fast-flow. Histology = NICH.
12	M	Ovoid, purple, elevated, central crusting (thigh) = RICH	Healing ulceration; regression left: ovoid; pink with pale halo = NICH. Resected @ 3 y	U/S fast-flow, Histology = NICH
13	F	Round, pink, bossed, 6 cm (knee) = RICH	Rapid regression over 1 y. Residuum = NICH (pale macule, telangiectasia, pallor, prominent draining veins). Unchanged between 1 and 7.5 y.	U/S fast-flow
14	M	Large, pink, bossed (thigh) = RICH	Rapid regression for 6 mo, leaving 16 cm diam. pale, pink plaque and coarse telangiectasia = NICH. Unchanged @ 6 y; excised in three stages.	U/S fast-flow. Histology = NICH
15	M	Bossed, purple, central depression, 6 cm (lateral knee) = RICH	Regression over 10 mo. Macule pallor, fine telangiectasia, two large veins = NICH.	U/S fast-flow

F, Female; *M*, male; *NICH*, noninvoluting congenital hemangioma; *RICH*, rapidly involuting congenital hemangioma; *U/S*, ultrasonography.

But not all congenital hemangiomas shrink in the first year—some do not regress at all. We called these noninvoluting congenital hemangioma (NICH), in contrast to rapidly involuting hemangioma (RICH).[2,3] Both NICH and RICH have an almost equal sex distribution, are usually solitary, and have a similar average diameter and a predilection for the same cutaneous locations, that is, the head or limbs near a joint. In contrast, common infantile hemangiomas exhibit female preponderance and variable morphology, and are often multiple, occuring anywhere in the body. NICH are round to ovoid, pink to purple, and often there is central or peripheral pallor of the overlying skin, punctuated by coarse telangiectasia. But unlike RICH and infantile hemangioma, NICH remains a fast-flow lesion, as documented by duplex Doppler examination. The MRI and angiographic findings in NICH are very similar to those of common hemangioma in the proliferative phase. In the past, these lesions have been mistaken as being a small arteriovenous malformation (AVM) or called "arteriolo-capillary malformation" because angiography demonstrates fast-flow and rapid filling, but without the early venous opacification typical of AVM. NICH usually can be excised easily without recurrence, unlike AVM.[3]

We refer to the 15 children described in this article as "missing links" because they suggest there is a biologic connection between the three types of vascular tumors, two congenital and one postnatal. There are both differences and similarities in the histologic patterns of NICH, RICH, and IH. NICH is

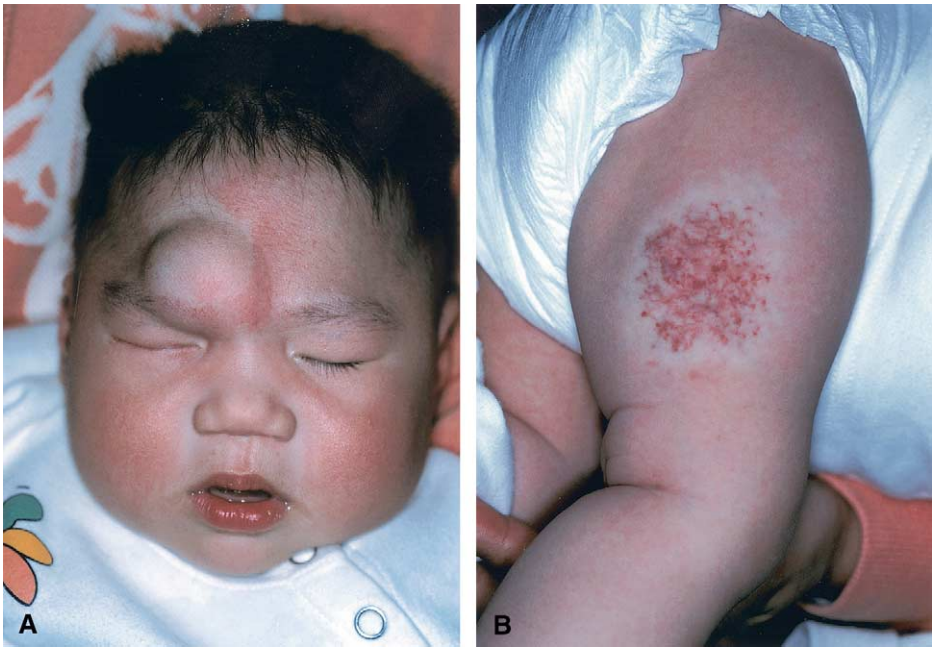

Fig 2. Link I, Patient 1. Infant with deep frontal IH **(A)** that plateaued at age 9 months and began to regress, and NICH on thigh at 9 months **(B)** that remained unchanged at 2 years.

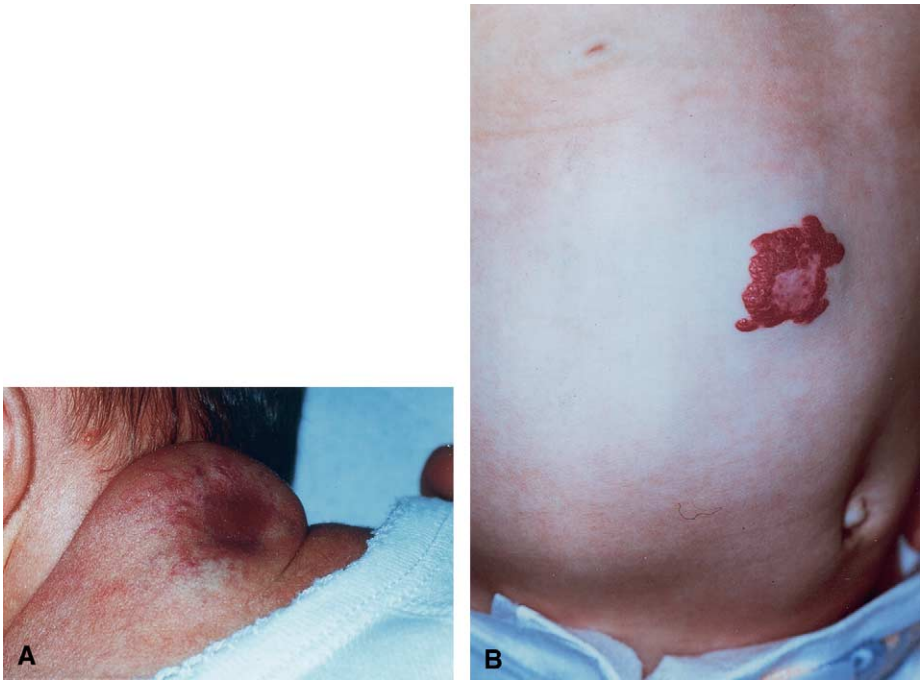

Fig 3. Link I, Patient 5. RICH of nape at birth, regressing at age 3 months **(A)** and "strawberry" IH on the abdomen that developed postnatally, also seen at age 3 months **(B).**

composed of large lobules of small vessels with intervening fibrosis and dermal arteriovenous microfistulae. A large stellate vessel is often seen in the center of these lobules, the endothelial cells can be hobnailed, and the basement membranes are thin.[2,3] RICH is composed of lobules of variable size, whereas the involuted areas lack lobules. Large extralobular vessels are present; the endothelium is moderately plump; basement membranes are thin in the early stage and thick

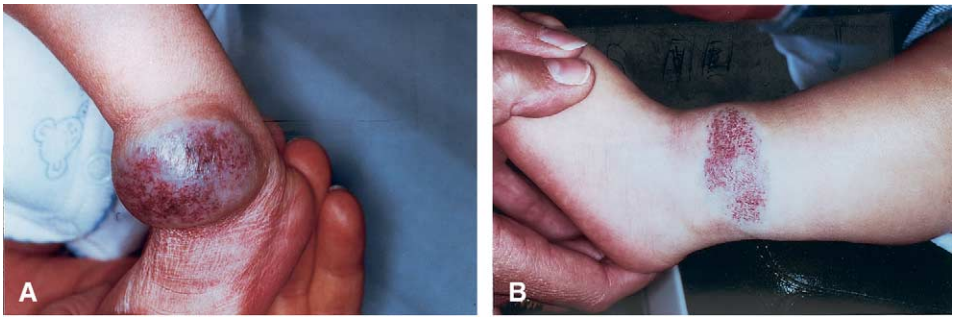

Fig 4. Link II, Patient 8. RICH of ankle at birth **(A)** and appearance after regression at 8 months of age **(B)**: telangiectatic plaque with pale halo, which looks like NICH. There was no change since age 3 months and thereafter.

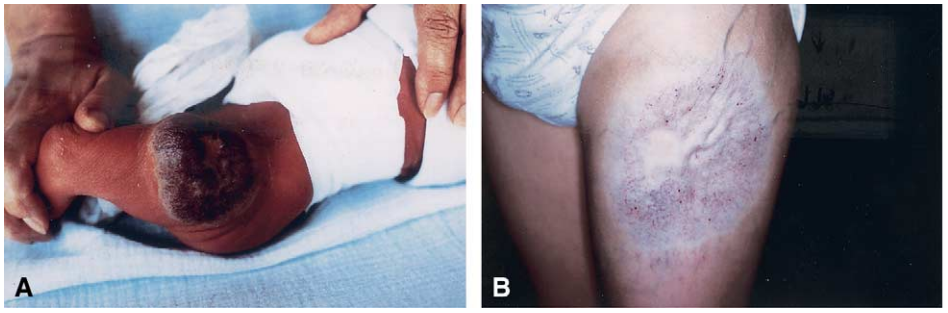

Fig 5. Link II, Patient 10. RICH of thigh at birth **(A)** and residual NICH-like lesion (with fast-flow) at 11 years **(B)**.

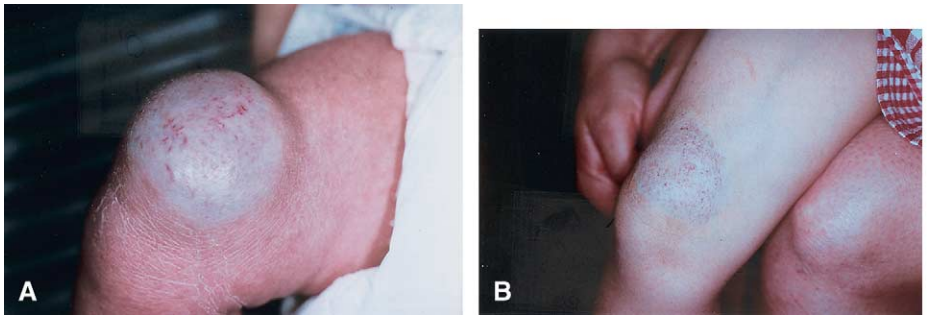

Fig 6. Link II, Patient 13. RICH of knee at birth **(A)** and 3 years later, NICH-like appearance with fast-flow, unchanged after age 8 months **(B)**.

after rapid regression.[2] IH in the proliferating phase is characterized by dense lobules of plump endothelial cells. In the involuting and involuted phases of IH, the endothelium flattens and the basement membranes thicken.

North and her colleagues suggested a fundamental connection between the microvessels that compose IH and the placental microvasculature, based on the unusual set of shared antigens: GLUTl, LeY, FcγRII, and merosin.[4,5] They hypothesized that IH arises either from emboli of placental cells or by a shift of the tumor's endothelium to the placental phenotype of fetal vessels.[5] However, neither NICH nor RICH are positive for GLUT1.[2,3,14] The absence of this marker suggests that the prenatal (congenital) tumors are biologically different from postnatal hemangioma. However, the observations in our 15 children tell a different story.

An immunohistochemical distinction does not necessarily mean the congenital forms are distinct vascular tumors. The presence of RICH or NICH and IH in the same child is presumptive evidence that

these 3 *vascular tumors* are part of a spectrum, if not a single entity. But because IH is very common, whereas NICH and RICH are extremely rare, there is the possibility that their concurrence is coincidental. In patients 1-5 there was either NICH (n = 4) or RICH (n = 1) and the subsequent appearance of a typical IH in another location. Thus, the coexistence of these vascular tumors, the rare type of prenatal onset, and the common type of postnatal onset is unlikely to be an aleatory phenomenon.

Our observations in the second group of linked patients (Nos. 6-15) raise the possibility that NICH could be a later stage of RICH. The evidence for this statement includes the appearance of the residual tumor, persistent fast-flow (documented by ultrasonography), and characteristic microscopic features in the resected specimens. Two such patients were described by Chiaverini et al[33] wherein a congenital hemangioma initially shrunk rapidly, but ceased and remained unchanged into adolescence as a telangiectatic round patch with a pale halo with fast-flow by ultrasonography. Histopathologic differences between the two types of congenital hemangioma have been described.[2] Nevertheless, more detailed prenatal and postnatal ultrasonic evaluations and postnatal observations of congenital tumors are needed to confirm the hypothesis that RICH can transform to NICH.

There is accumulating evidence that hemangioma of infancy is caused by somatic mutation(s) in a single, endothelial cell progenitor with ensuing clonal expansion.[34,35] Perhaps different mutations account for the behavioral divergence, either rapid involution or noninvolution, and the absence of GLUT1 immunoreactivity in the congenital vascular tumors (RICH and NICH).

Our findings in this series of infants with congenital vascular tumors suggest an association or linkage with postnatal hemangioma, the common lesion of infancy. Granted, we have raised more questions than provided answers. Despite our bias toward a unified theory of origin for these fetal and infantile vascular tumors, for the time being it is best to underscore their clinical distinctiveness. In so doing, we can give parents a prognosis and therapeutic plan, specific to each of the 3 vascular tumors, whatever might be their possible pathogenic relationship.

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