Morphological characterization of infantile hemangiomas: An Indian study
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Abstract

Context: Vascular tumors of infancy and childhood consist of a number of clinicopathologically distinct entities. Infantile hemangiomas (IH) constitute the bulk of these tumors. As they are seldom biopsied, we do not encounter an opportunity to study them, and this is evident from the paucity of reported cases in pathology literature from India. Clinicians and pathologists alike have traditionally tended to lump these tumors, under overly generic terms like capillary hemangioma which do little to guide proper clinical management.

Aims: To delineate the morphological features that characterize IHs and outline the morphological changes seen in different phases of evolution of this tumor.

Subjects and Methods: We characterized 21 cases of IHs over a period of 60-months. Mast cells were counted in 10 fields of high density, and mast cell density per square millimeter area was calculated.

Results: Female to male ratio was 1:1.6. Head and neck were the most common region involved (71.4%). Morphological features were described. Mast cell density/square millimeter area ranged from 126.9 to 285.7. Spearman correlation coefficient was 0.681 (P = 0.676).

Statistical Analysis: Spearman correlation coefficient was used to analyze the relationship between mast cell numbers and the age of the lesion.

Conclusions: Morphological features seen on routine microscopy can easily help distinguish a lobular capillary hemangioma from an IH or a congenital hemangioma even in the absence of relevant clinical details, pointing to a need for looking beyond using a generic term of capillary hemangioma.

Introduction

Hemangioma of infancy or Infantile hemangioma (IH) is a form of capillary hemangioma. It is characterized by proliferation of benign capillaries, perinatal or congenital in onset, rapid proliferation in the 1st year followed by spontaneous regression.¹ From as high as 10-12% of children, to as low as 1 in 200 live births, the reported incidence of IH varies. However, texts agree on the point that IH is the most common tumor of infancy.¹⁻⁴

Pathologists seldom encounter an IH due to the practice of active non-intervention by treating clinicians in uncomplicated hemangiomas. Complications encountered include ulceration, hemorrhage, infection, heart failure, impairment of vision, interference with feeding, and obstruction of the external auditory meatus.¹⁻⁴ Medical or surgical intervention is necessary in IHs with complications. Numerous options available to treating physicians range from topical corticosteroids to surgical excision, which include interferon-alpha, bleomycin, cyclophosphamide, intraläsional sclerosant injection, embolization to surgical excision.¹⁻⁴

To our knowledge, there has been no study which focuses on morphological features of IHs in India. Although there have been a few studies which focus on intervention in cases of IHs,¹⁻⁹ Our study aims to delineate the morphological features that characterize IHs and outline changes seen in different phases of evolution of this tumor.
### Results

The age range was 6 months to 12 years (mean 46 months). This is the age at presentation but the lesions were present since birth in 13 cases and appeared at various months following birth in the other eight cases. Female to male ratio was 1:1.6. Head and neck were the most common region involved (71.4%), and most of them were recognized by clinicians as hemangioma except four cases.

Six cases presented with complication in the form of ulceration and hence were operated. Case 1 was a case of cleft lip complicated by an IH [Figure 1a] which was present on either side of the cleft and extended on the nose. Partial excision of the lesion was done to enable repair of the cleft lip.

Case 2 [Figure 1b] had lead to a bulbous deformity of the nose; excision was done fearing adverse psychological effects on the child who had just begun schooling. Progression of the lesion was an indication for surgery in two cases. No indication for surgery was mentioned in other cases. None of the cases showed systemic complications or association with syndromes.

Case 13 was operated for a clinical diagnosis of cystic hygroma and resected only partly. Case 21 was operated for ptosis correction by an ophthalmologist [Figure 1c]. Submandibular salivary gland was involved in the first, and lacrimal gland was the site of involvement in the second case [Figure 1d].

On gross, the average size of the lesion was 2.25 cm at its greatest dimension (median 1.5 cm). All lesions were irregular, poorly circumscribed with overlying skin having a wrinkled appearance; ulceration was grossly identifiable in four of the cases. Cut section of the lesions showed a pale pink lobulated appearance with interspersed gray-white areas.

Histologically, the lesions showed a multilobular pattern with masses of endothelial cells occupying the dermis and subcutis [Figure 1e]. About 10 lesions were in involuting stage with cases showing varying degrees of involution. Densely cellular areas were present toward center of the lesion with hardly any lumen formation seen [Figure 2a]. The endothelial cells were seen wrapping around adnexal structures and residual acini. Toward periphery the lobular architecture was more evident and capillaries with well-formed lumina were present. The cells in these areas were flattened in comparison to the center of the lesion. The basement membrane and lumina of capillaries were highlighted using reticulin stain [Figure 2b] and capillary architecture could be recognized even in the center of the lesion which otherwise appeared as a mass of endothelial cells on H and E sections.

Lesion in the 7-year-old child was the most involuted of all as it showed well-formed capillaries throughout the lesion with flattened endothelium and thick basement membranes and marked fibrosis in comparison to other lesions which showed such a change only at the periphery [Figure 2c].

### Subjects and Methods

All cases of IHs diagnosed in our institution over the period of 5 years from 2009 to 2013 were included in this study. All the case details available in the request forms and case records when available were collected [Table 1]. Sections were stained with H and E staining. Reticulin stain was utilized to better delineate the vascular nature of the lesions. Acidified toluidine blue stain at pH 3.2 was used to identify mast cells in the hemangiomas. Mast cells were counted in 10 fields of high density at ×450 magnification, and mast cell density per square millimeter area was calculated. Spearman correlation coefficient was determined to find if there was any correlation between duration of lesion and mast cell density.

### Table 1: Case details

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Duration</th>
<th>Clinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 months</td>
<td>Male</td>
<td>Upper lip</td>
<td>5 months 14 days</td>
<td>Strawberry hemangioma</td>
</tr>
<tr>
<td>2</td>
<td>3 years</td>
<td>Female</td>
<td>Nose tip</td>
<td>2 years 10 months</td>
<td>Strawberry hemangioma</td>
</tr>
<tr>
<td>3</td>
<td>8 years</td>
<td>Male</td>
<td>Lt ring finger</td>
<td>Since birth</td>
<td>AV malformation</td>
</tr>
<tr>
<td>4</td>
<td>2 years</td>
<td>Female</td>
<td>Malar region</td>
<td>Since birth</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>5</td>
<td>6 months</td>
<td>Female</td>
<td>Labia majora</td>
<td>Since birth</td>
<td>Strawberry hemangioma</td>
</tr>
<tr>
<td>6</td>
<td>1 years</td>
<td>Male</td>
<td>Back</td>
<td>Since birth</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>7</td>
<td>1 years</td>
<td>Female</td>
<td>Forehead</td>
<td>Since birth</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>8</td>
<td>1 years</td>
<td>Male</td>
<td>Cheek</td>
<td>Since birth</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>9</td>
<td>2 years</td>
<td>Female</td>
<td>Scalp</td>
<td>Since birth</td>
<td>Strawberry hemangioma</td>
</tr>
<tr>
<td>10</td>
<td>7 years</td>
<td>Female</td>
<td>Chest wall</td>
<td>Since birth</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>11</td>
<td>5 months</td>
<td>Male</td>
<td>Axilla</td>
<td>Since birth</td>
<td>Strawberry hemangioma</td>
</tr>
<tr>
<td>12</td>
<td>1 years</td>
<td>Male</td>
<td>Scalp</td>
<td>Since 6 months</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>13</td>
<td>6 months</td>
<td>Male</td>
<td>Salivary gland</td>
<td>Since birth</td>
<td>Cystic hygroma</td>
</tr>
<tr>
<td>14</td>
<td>8 years</td>
<td>Male</td>
<td>Scalp</td>
<td>Since birth</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>15</td>
<td>5 years</td>
<td>Male</td>
<td>Scalp</td>
<td>Since 4 years</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>16</td>
<td>5 years</td>
<td>Male</td>
<td>Chest wall</td>
<td>Since 2 years</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>17</td>
<td>11 years</td>
<td>Male</td>
<td>Scalp</td>
<td>Since 8 years</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>18</td>
<td>8 years</td>
<td>Female</td>
<td>Scalp</td>
<td>Since 5 years</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>19</td>
<td>3 years</td>
<td>Female</td>
<td>Eyelid</td>
<td>Since birth</td>
<td>Hemangioma</td>
</tr>
<tr>
<td>20</td>
<td>12 years</td>
<td>Male</td>
<td>Chin</td>
<td>Since 10 years</td>
<td>Lipoma</td>
</tr>
<tr>
<td>21</td>
<td>9 months</td>
<td>Male</td>
<td>Lacrimal gland</td>
<td>Since birth</td>
<td>Pleomorphic adenoma</td>
</tr>
</tbody>
</table>

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IHs were not circumscribed even on microscopy and showed endothelial cells wrapping around the adnexal structures, sheets of endothelial cells investing in between the mature adipocytes in the subcutis. Perineurial invasion was present in five cases [Figure 1f].

Case 3 was unique in both clinical behavior and its morphological features. It was a diffuse lesion on the left ring finger with a ridged surface and prominent (telangiectatic) pulsating vessels seen on the surface. The lesion had been progressively increasing in size throughout its course. These findings were very much contrary to the natural history of an IH. It was diagnosed as an arteriovenous (AV) malformation clinically.

Microscopically, the lesion was in the dermis and subcutis. Capillaries with rounded lumina arranged in a back to back fashion forming lobules were seen with areas showing only masses of endothelial cells. Many lobules showed a central vessel with thickened wall, Verhoeff elastic stain highlighted the elastic fibers in these central vessels pointing to the possibility of these being arterialized veins or AV fistulas. Groups of capillaries were seen garlanding the wall of a medium sized artery at the center of the lesion. Perineurial infiltration by endothelial cells was also present. These features favored a non-involuting congenital hemangioma (NICH) rather than IH.

Mast cell density/square millimeter area was calculated [Figure 2d]. It ranged from 126.9 to 285.7. Duration ranged from 5 months to 12 years. Spearman correlation coefficient was 0.681 ($p = 0.676$). Even though not significant it shows a good correlation between duration and mast cell numbers.

**Discussion**

Several studies in the recent past have determined the demographic characteristics of IH [Table 2]. They have explored and attempted at subclassification made. However, the most significant has been the work that is directed toward determining the pathogenesis of these lesions and is the focus of most of the recent reviews. It is the hypotheses put forward for pathogenesis that seems to have spurred the studies.
Table 2: Comparison of clinical data in IH

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Chiller et al. 2002</th>
<th>Dadras et al. 2004</th>
<th>Present study in 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>327</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>Age range (months)</td>
<td>2-158.3</td>
<td>2-60</td>
<td>6-144</td>
</tr>
<tr>
<td>Mean age at presentation</td>
<td>11.8 months</td>
<td>26.3 months</td>
<td>46 months</td>
</tr>
<tr>
<td>Median age at presentation</td>
<td>4.5 years</td>
<td>22 months</td>
<td>1 year</td>
</tr>
<tr>
<td>Sex: Male to Female</td>
<td>1:3.8</td>
<td>1:6</td>
<td>1:6.1</td>
</tr>
<tr>
<td>Lesion at birth</td>
<td>36%</td>
<td>-</td>
<td>61.9%</td>
</tr>
<tr>
<td>Appearing in first month</td>
<td>40%</td>
<td>-</td>
<td>81.8%</td>
</tr>
<tr>
<td>Commonest location</td>
<td>Head and neck</td>
<td>Head and neck</td>
<td>Head and neck</td>
</tr>
</tbody>
</table>

IH: Infantile hemangiomas

Prematurity and low birth weight (LBW) are associated with increased incidence of IHs. A recent study had found that LBW is the most significant risk factor; for every 500 g decrease in birth weight, the risk of IH increased by 40%. A significant proportion of LBW infants is premature. National Vital Statistic System data found 20% of infants to be premature and 6% of patients very premature, thus suggesting that an imbalance of control mechanisms may result from prematurely removing a developing fetus from maternal and placental influences.[12,13] In our study, we could not source data regarding birth weight of our patients.

IHs are either present at birth or present within the first few months of life. In our study, 61.9% (13/21) patients had a lesion at birth while in another study compared herein 36% of lesions were present at birth.[10] Characteristic of appearing sometime after birth may be the cause for variable incidence reported in various studies, according to a systematic review. The authors of this review suggest that careful skin examination must be carried out for a minimum of 3-4 months of age, by which many IHs become apparent.[10] Keeping with studies that put hemangioma between 1% and 10%, true incidence may be somewhere midway.[19,20]

Age at presentation is different from when lesion was the first noticed. It is the rapid growth of lesion or complications associated with it that form the cause for presentation, so also the treatment. Average age at presentation in our study was 46 months, as against 11.8 months and 26.3 months noted in other two studies. The age at presentation could differ with patient awareness and availability of health services. We have compared with studies in developed country (USA) due to non-availability of studies to compare with the local population.[10,11]

Most studies agree that females are more commonly affected than males; the ratio for female to male ranging from 1.4:1 to 3:1. However, in our study, the ratio was 1:1.6, not similar to other studies.[12] This could be probably related to the attitude of parents in seeking treatment for the male child.

Patient with IHs is more likely to be female, white non-Hispanic, premature and products of multiple gestations. Prenatal association include older maternal age, placenta previa and pre-eclampsia.[12]

IHs can be classified clinically as localized, segmental, indeterminate and multifocal. Localized arises from a central focus, segmental covers an anatomic territory with indeterminate being between the two. Higher risk of complications and associated structural abnormalities are seen in a segmental distribution. Most hemangiomas are located in head and neck region, involving the face most commonly. In a study of segmental and indeterminate hemangiomas, 165 of total 294 lesions studied were facial hemangiomas. In another study of 28 IHs, 83.3% and 100% of proliferative phase and involuting phase IHs were located in the head and neck region, respectively.[11,13] Involvement of glandular structures is seldom encountered and reported. Isolated lesions without associated anomalies are sometimes identified only after microscopic examination, as in two of our cases involving salivary and lacrimal gland.

IHs in the face, especially segmental hemangiomas are not random in their distribution but correspond to known developmental units such as the mandibular and maxillary prominences, Haggstrom et al. identified four segments as frontotemporal, maxillary, mandibular, and frontonasal.[13]

Clinical photographs were available in six of our cases, one case of IH involving right side of the upper lip and the nose, showed partial segmental involvement. The lesion was associated with a right-sided cleft lip and was present on either side of the cleft but not involving the philtrum, thus respecting facial development segments. This finding has also been observed in the study of Haggstrom et al.[13]

Segmental hemangiomas are more likely to be associated with abnormalities, commonest being PHACE syndrome. Congenital abnormalities, spinal involvement and deeper structure involvement are also seen. It has also been shown that associated anomalies increase as the size of the lesion increases. The cleft lip was the associated abnormality in one of our cases; this has only rarely been reported as an associated abnormality with only four cases reported in the literature to our knowledge.[17]

Various associated complications are the ones that may convince the clinician to contemplate a surgical treatment instead of opting for a conservative treatment. Various complications reported have been ulceration, bleeding (usually minor), cutaneous infections, and pain. Rare complication includes high output cardiac failure without structural heart anomalies, airway compromise, severe scarring, inability to turn the head and neck, difficulty in oral intake, auditory canal occlusion; ophthalmologic impairment.[10] In our study, ulceration was seen in six cases and ptosis in one case (was the only associated complication).

A grouping for IHs based on their clinical course, which is reflected in their histopathological appearance as well, proposed by Mulliken and Glowacki is the most widely accepted. They group IHs into proliferating phase, involuting phase and involuted phase. Proliferating lesions are the ones showing a rapid growth clinically usually during the first 3-6 months of age, but may extend up to 12 months of age, Histologically, mass of plump endothelial cells lining inconspicuous vascular...
lumina highlighted only by reticulin stain are seen. Maturation commences at the periphery of the lesion gradually involving all the zones. With time, there is a progressive flattening of the endothelium and thickening of the basement membrane.[21]

Involution, once initiated, progresses at a consistent rate, showing complete resolution in 50% of children by 5 years and 70% by 7 years of age, although involution has been noted up to 12 years. In a study, prolonged growth was observed in IHs with a deep component and segmental morphologic characteristics, thus bolstering an attempt to subgroup hemangiomas based on their spatial configurations.[21,22]

Involution is completed by a progressive diffuse interstitial fibrosis and is believed to be mediated by way of apoptosis. Fibrofatty tissue interspersed with dense collagen and reticular fibres replace the previous vascular network.

Perineurial invasion in cellular IHs has often been overlooked. This may be because many cellular capillary hemangiomas are seldom treated surgically as their natural history is to regress spontaneously over time. Hence, when surgical treatment is undertaken, there is little doubt about the clinical and histological diagnosis especially when the patients are infants or children. The perineurial invasion becomes a worrisome finding when lesions persist and are excised surgically. With atypical features, the possibility of angiosarcoma could be considered in differential diagnosis, even though it is unwarranted.[23]

Eight of the 21 cases showed perineurial invasion. Even though neural involvement was present, the pain was not recorded as a symptom in any of these patients. This is in keeping with non-destruction, possibly symbiotic process. It has been proposed that role played by nerves is more than just “innocent bystanders” trapped by proliferating cells. According to this theory nerves, might interact actively through secretion of growth factors with surrounding tissues; thereby involving cells to proliferate and differentiate and in the process of so doing become entrapped by them.[24]

Mast cell numbers are increased in hemangiomas, with the highest counts observed in the involuting phase. A four-fold, increase of mast cells numbers in hemangioma is seen subsequent to steroid – induced accelerated regression. These findings suggest that certain products secreted by mast cells may play an active role in regression of hemangiomas. In our study, we found an indication toward a possible relation to mast cell numbers and duration of lesions (Spearman correlation coefficient 0.681) prompting a need for more cases to be studied before a positive correlation could be established. More importantly mast cell numbers in involuting IH was significantly higher than in lobular capillary hemangiomas.[24,25]

The role of mast cells in the progression of hemangiomas is likely to be complex, and it may involve stimulating angiogenesis in the proliferative phase but inhibiting it in later phases.[25]

With the intensive study of IHs, researchers noticed exceptions, cases which would not comply with the natural evolutionary progression of IHs. These lesions which were fully grown at birth, having arisen in utero were designated as congenital hemangiomas.[26]

Lumped together in the past with IHs and vascular malformation, two clinical subtypes have now been identified in congenital hemangiomas: Rapidly involuting congenital hemangioma (RICH) and NICH.

RICH usually shrinks in the 1st year of life, a time course that is more rapid than that of IH. Both RICH and NICH do not show rapid neonatal growth; variably sized lobules are seen consisting of small vascular channels that are usually fairly regular with prominent draining channels in center. Basement membrane thickens as the lesion ages.[27]

NICH is a rare variant of CH, with female preponderance and same anatomic distribution as IH. Three predisposed sites described were the mandibular border, upper thigh, near the knee and arm around the elbow. Coarse telangiectasia, pale rim and areas of intermingled pallor were described as characteristics and unique features clinically.[28]

NICH never disappear or involute. They remain unchanged except for proportional growth and appearances of increased draining veins in the periphery of the lesion. Imaging will confirm fast flow, and magnetic resonance imaging will show hyperintensity of T2 weighted sequences with flow voids similar to IH. Arteriography examination reveals arterial like feeders, a tumor like capillary blush with small arterial channels. Early venous drainage is not seen, which differentiates these lesions from AV malformations or AV fistula on angiography.[29]

No excessive bleeding from resection margins was noticed on excision of NICH unlike in AV malformation. Neither was recurrence noticed in CH, unlike in AV malformations which are incompletely excised.[28]

Two features which have been proposed to identify NICH on microscopy are the presence of large lobules of small vessels with AV or arterio-lymphatic micro fistulae, and/or hobnailed endothelial cells. GLUT-1 positivity on immunohistochemistry has emerged as a major distinguishing factor between IH which invariably show GLUT–1 positivity and CHs.[30]

Another entity described as being distinct by its authors from IH, NICH and RICH has been congenital non-progressive hemangioma (CNPH). In a study of 43 congenital and early vascular lesions over a period of 20 years, 5 coherent categories were defined with the majority being IHs (25); pyogenic granuloma (10) tufted angioma (1) infantile kaposiform hemangioendothelioma being others; besides 6 cases of CNPH.[31]

North et al.[31] in their article contended that overlying epidermis is atrophic in CNPH. GLUT-1 and LeY expression was absent, extramedullary hematopoiesis was observed in 5 of the 6 lesions. Intraneural involvement was conspicuous by its absence, which is otherwise a common finding in IHs. Even though authors successfully distinguish CNPH from IH, no convincing argument is put forward to distinguish CNPH from more firmly established NICH and RICH. Further, all patients with CNPH were operated at <3 months of age, thus little is known of the natural history of those lesions. Moreover, features described are all found in RICH, and it is possible that these lesions might be just RICHs.[31]
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Pathogenesis of capillary hemangiomas remains a hot topic receiving the widespread attention of researchers. For a pathologist to distinguish a lobular capillary hemangioma from an IH or a congenital hemangioma is important, pointing to a need for looking beyond using a generic term of capillary hemangioma, and study of a large cohort of cases.

Conclusion
To characterize a tumor would be incomplete without its cell of origin, morphology is the cornerstone for this process. Ongoing work in defining the molecular basis through IHC, ultra structural studies and molecular techniques is yet to yield results. As we learn more about vascular neoplasms, our understanding of the process of vasculogenesis is likely to improve, thus opening up new horizons for treatment.

References