On infantile hemangiomas
Hoornweg, M.J.

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Malignant differential diagnosis in children referred for infantile hemangioma
Abstract

Background and Aim Infants with tumors can be misdiagnosed as having infantile hemangioma and this diagnosis can lead to delay or omission of proper treatment. The purpose of this study was to determine the malignant differential diagnosis in pediatric patients referred for an “infantile hemangioma” and to assess how the misdiagnosis was reached.

Methods The database of the Department of Plastic, Reconstructive and Hand surgery of the Academic Medical Center in Amsterdam was reviewed for children referred with a diagnosis of infantile hemangioma from April, 2003, through December, 2009. Their records were studied to determine the definitive diagnosis. Characteristics of the children with malignant diagnoses and of their diagnostic process were retrospectively analyzed.

Results The referral diagnosis “hemangioma” was recorded for 251 girls and 172 boys and was confirmed in 377 of these 423 children (89%). Thirty-nine of the other 46 children were re-diagnosed with a single or combined form of vascular malformations (n = 31 or 7%) or other benign anomalies (n = 8 or 2%). The seven remaining children (2%) were diagnosed with a rhabdomyosarcoma (n = 2), a sarcoma (n = 1), a poorly differentiated round and spool cell sarcoma (n = 1), a nerve sheath sarcoma (n = 1), a dermatofibrosarcoma protuberans (n = 1), or a lymphoma (n = 1).

Conclusions Early age malignant tumors can mimic benign infantile hemangioma. In cases where the diagnosis of infantile hemangioma is equivocal, biopsy has to be performed in a specialized center to prevent delay or omission of proper treatment.
Introduction

Infantile hemangiomas (IH) are the most common tumor of infancy, with a prevalence of 10%. If noticed at birth (20-30%), only precursor lesions such as telangiectasia or a blanched area, are present. IH more typically appear during the first six months of life and immediately undergo growth during a proliferation phase that lasts three months on average. They are located superficially, deeply, or combined superficially and deeply. IH are not painful unless they ulcerate, which happens predominately during the proliferation phase in 16% of cases. The proliferation phase is followed by an involution phase that sets in at an average age of 18 months. During this phase, the cellularity, size, and turgidity decreases and the color fades to a grey hue, usually starting in the center of the tumor. Once started, this regression progresses at a consistent rate, resulting in complete resolution by the age of 5 years in 50% of children, and by the age of 7 in 70% per cent. In 93% per cent of children with IH, the diagnosis can be made based on the clinical features by the use of the classification of Mulliken and Glowacki that was modified and adopted by the International Society for Study of Vascular Anomalies. In these cases, a ‘wait and watch’ policy may be adopted or, when indicated by secondary symptoms, treatment should start. In the remaining 7% per cent, additional investigations such as ultrasonography, MRI, or pathological examination need to be performed to differentiate IH from other benign or malignant tumors. Frieden et al recently recorded a comprehensive benign and malignant differential diagnosis of IH (Table 1). They cautioned that their list of diagnosis did not exclude the possibility that other, as yet unreported IH mimics exists.

Table 1 Malignant differential diagnosis as suggested by Frieden et al extended with our observations (added in italics)

Solitary lesions
- Dermatofibrosarcoma protuberans
- Giant cell fibroblastoma
- Infantile fibrosarcoma
- Rhabdomyosarcoma
- Lymphoblastic lymphoma
- Poorly differentiated sarcoma
- Malignant tumor of the sheath of a nerve
- Poorly differentiated round and spool cell malignancy

Multifocal diseases
- Metastatic rhabdomyosarcoma
- (Metastatic) neuroblastoma
- Congenital leukaemia cutis
- Peripheral primitive neuroectodermal tumor
- Adrenocortical carcinoma
- Undifferentiated sarcoma
Over the last decade, we were confronted with malignant IH mimics that have not been reported to date. Furthermore, Frieden et al did not illustrate all of the malignant mimics they suggested. In case of misdiagnosis of a malignancy as an IH the ‘wait and watch’ policy leads to delay or omission of optimal treatment. Therefore, we report on our patients with a malignancy that was initially presented under the diagnosis “infantile hemangioma”.

Materials and Methods

Approval for this retrospective study was obtained from the Committee on Clinical Investigation at the Academic Medical Center (AMC) in Amsterdam, The Netherlands. The medical records of all children under 18 years of age, who were initially referred with the diagnosis “infantile hemangioma” to the Department of Plastic, Reconstructive and Hand surgery in the Academic Medical Center (AMC) from April, 2003, through December, 2009, were assessed. From these, we extracted the definitive diagnosis and the sex, age of onset, and age at referral of the child. The age of onset was defined as the month of life in which the tumor was first noticed. In cases where the tumor presented at birth, this age was recorded as 0 months.

The complete diagnostic pathway of anamnesis, physical examination, all types of investigations (e.g. MRI or ultrasound), and the pathological examination of the tumor was reconstructed in cases where the definitive diagnosis was a malignancy. For this sub-group, we calculated the delay of the definitive diagnosis defined as the period of time between the initial presentation of the skin anomaly that was incorrectly labeled as “infantile hemangioma” and the initiation of further investigation because of doubt regarding this initial diagnosis.

Results are presented in descriptive statistics. The Kruskal-Wallis test, an ANOVA test with a post hoc-test (Turkey HSD), was applied to compare the age at onset of the skin anomaly and that at referral in children with IH with those in the children with other definitive diagnoses. A two-tailed value of \( p < 0.05 \) was considered as statistically significant. Statistical analysis was performed using the SPSS software package (version 16.0; SPSS Inc., Chicago, USA).

Results

Differential diagnosis and demographic characteristics

The referral diagnosis “infantile hemangioma” was recorded for 423 children. This diagnosis was confirmed in 377 of these children (89 per cent). Thirty-nine of the other 46 children were re-diagnosed with a single or combined form of vascular malformations (n = 31 or 7 per cent) or other benign anomalies (n = 8 or 2 per cent) (Table 2). Malignant diagnoses were reached in the remaining 7 children (2 per cent). These consisted of
Malignant differential diagnosis in children referred for infantile hemangioma

a rhabdomyosarcoma (n = 2), a sarcoma (n = 1), a poorly differentiated round and
spool cell sarcoma (n = 1), a nerve sheath sarcoma (n = 1) a dermatofibrosarcoma
protuberans (n = 1), or a lymphoma (n = 1) (Figures 1 – 7, See Appendices).
Two-hundred and forty-three of the 377 children with an IH (64 per cent), 18 of the 31
children with a vascular malformation (58 per cent), three of the eight patients with an
other benign tumor (38 per cent), and five of the seven patients with a malignancy (71
per cent) were female.
The median age of onset in children with IH was 4 months (range, 1 – 9 months) and
the median age of these children at referral was 6 months (range, 1 – 15 months). These
ages at onset and at referral differed significantly with those of children with a vascular
malformation (p < 0.000 and p < 0.000 respectively) or an other benign tumor (p <
0.001 and p < 0.001 respectively), but not with those of children with a malignancy (p
= 0.340 and p = 0.705 respectively) (Table 2).

### Table 2

| Gender, age at onset of anomaly, and age at referral to our team observed in the 423 children with the referral diagnosis “infantile hemangioma” |
|-------------------------------------------------|------------------|------------------|------------------|
| Gender: male ratio                              | Infantile hemangioma (n = 377) | Other Vascular anomaly (n = 31) | Other Benign tumor (n = 8) | Malignancy (n = 7) |
| Female: male ratio                              | 243 : 134         | 18 : 12           | 3 : 5             | 5 : 2             |
| Median age at onset (months)                    | 4                | 10               | 15               | 0.5               |
| Range of age at onset                           | 1 - 9            | 0 – 105          | 1 – 58           | 0 - 60            |
| Median age at referral (months)                 | 6                | 13               | 16               | 1                |
| Range of age at referral                        | 1 - 15           | 3 - 160          | 1 - 60           | 0 - 62           |

### Work-up to referral of the alleged IH

In four of the seven children (cases C, D, F and G), false initial diagnostic conclusions
were reached by the referring physician after anamnesis and physical examination. In
two of these children (case F and G), the ultrasonography ordered by their physician
had been inconclusive.
In two of the other children (cases A and B), the false initial diagnosis reached after
anamnesis and physical examination where, even, supported by ultrasonography.
The one remaining child (case E) had had multiple investigations elsewhere because of
doubt regarding the initial diagnosis of IH. These had been inconclusive and the child
was referred to us for a second opinion.

### Work-up to definitive diagnosis of malignancies

After referral, we additionally performed ultrasonographies in 3 children (cases A, C
and F) and MRI’s in 6 children (cases A, B, C, D, F, and G). In one case (D), plain film
radiography and CT scan were executed to assess the extension of the anomaly.
The ultrasonography was consistent with IH in one case (A) and indecisive in another (C). In the remaining case (F), the ultrasonography was not consistent with IH and MRI was advised. The MRI was consistent with IH in one case (A) and indecisive in another (B). It raises suspicion of malignancy in the remaining cases (D, C, F, G). The plain film radiography and CT scan provided information on the extension of the tumor, but not on its character.

The ultrasonography, plain film radiography, MRI and MR-angiography previously performed in case E were reassessed by our team. Based on these and the clinical presentation, it was concluded that the anomaly was not an IH.

Biopsies for pathological examination were obtained and led to the definitive diagnosis in all children.

After the definitive diagnosis was reached, five plain film radiographies, three CT scans, and three scintigraphies were made to exclude metastasis of the malignancy.

**Delay to definitive diagnosis of malignancies**

The three children with a congenital malignancy were referred immediately after birth and no delay was observed. The mean delay of referral in the remaining four children with a malignancy was 11 months (range, 0 – 37 months) (Table 3).

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at onset of tumor (months)</th>
<th>Age at referral (months)</th>
<th>Delay (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>60</td>
<td>62</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>6</td>
<td>43</td>
<td>37</td>
</tr>
<tr>
<td>C</td>
<td>20</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>E</td>
<td>0</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>F</td>
<td>0.5</td>
<td>4.5</td>
<td>4</td>
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<tr>
<td>G</td>
<td>0</td>
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</table>

**Discussion**

**Diagnostic pitfalls of IH**

Because IH is a diagnosis that defines a benign vascular tumor with a typical clinical course, this diagnosis can be reached based solely on anamnesis and physical examination in 93 per cent of cases. The anamnesis should confirm the lack of presence of the anomaly at birth, the occurrence of a proliferation and involution phase with the associated presence of volume changes, and the lack of pain or secretion in cases where no ulceration of the anomaly has occurred. At physical examination,
increase of resilience and increase followed by decrease of volume over time, lack of souffles, ‘thrill’ or pulsations, lack of flebolits, and lack of hyper- or hypotrophy are to be observed, as expected in cases of IH.\textsuperscript{3,10}

As Frieden et al stressed\textsuperscript{13}, the five risk factors of early age malignancies suggested by Knight and Reiner\textsuperscript{14} and employed by Coffin and Dehner\textsuperscript{15} largely overlap with the diagnostic clues for IH. As such, an onset in the neonatal period, a history of rapid or progressive growth, skin ulceration, location deep to the fascia, and a firm mass greater than 3 cm in diameter are clues that are congruent with both IH, and a malignancy. Rather than diagnostic clues, therefore, Frieden et al suggested five common themes regarding IH.\textsuperscript{13} First, an IH typically presents and increases during the first six months of life even though a precursor lesion may present at birth.\textsuperscript{5} Like presence at birth or growth in uteri, occurrence or growth after the age of one year should be considered alarming clues. We add that, in cases where the congenital tumor has a vascular appearance, the differential diagnosis should also include the rapidly involuting and non- involuting congenital hemangiomas (RICH and NICH). Unlike IH, RICH and NICH both have their growth phase in uteri and reach their maximum size before or at birth.\textsuperscript{16} Subsequently, a RICH involutes rapidly by 6 to 10 months, whereas a NICH does not involute at all. But even in these cases, biopsies are still needed to rule out other neoplasms even though typical sonographic features are described.\textsuperscript{17} Second, Frieden et al stressed that the clinical appearance of vascularity cannot be assumed to indicate the diagnosis of IH.\textsuperscript{13} For example, teleangiectasias may be seen as a precursor lesion of IH, in the late involution stage or at the borders of the IH but do not predominately cover the surface of typical IH (Figure 1, See Appendices). We would further add that signs of pain, continuous bleeding or ulcerations, and rapid growth of the tumor that is incongruent with the natural growth of the child are indications for referral.\textsuperscript{1,3,18}

Third, multiple IHs mostly occur superficial and in the first few weeks of life. Deeper located multiple anomalies should raise alarm. Fourth, IHs may feel firm on palpation during the proliferation phase and softer during the regression phase. Regardless of the depths of their location, they never feel rock hard or fixed to the underlying fascia. Aberrant findings on palpation necessitate additional evaluation. Finally, we agree with Frieden that MR or ultrasonographic findings of high vascular flow cannot be assumed to support the diagnosis of IH and that, ultimately, an incisional or excisional biopsy may be needed to adequately reach the diagnosis.

In all cases where anamnesis and physical examination does not unequivocally indicate the diagnosis of IH, as well as in all cases where the initially consulted physician lacks adequate expertise with IH, the child should be referred to an experienced vascular anomaly team to rule out differential diagnoses. Still, additional imaging investigations may indeed not be helpful to differentiate IH from malignant tumors as is confirmed in our study.\textsuperscript{18,19} Because of its non-invasive nature and low costs, ultrasonography may be suitable as a first-line screening tool to discriminate IH from other soft-tissue
tumors\textsuperscript{3,20}, but even an experienced ultrasonographer can have trouble distinguishing a IH.\textsuperscript{20,21} Likewise, MRI may be useful to differentiate between an IH and a vascular malformation\textsuperscript{22,23}, but cannot be conclusive as to whether a lesion is benign or malign.\textsuperscript{24} At best, it can guide the biopsy to make a definite diagnosis by differentiating necrosis from solid tissue.\textsuperscript{26} The accurateness of interpretation of such additional imaging studies, moreover, correlates with accurateness of the clinical findings.\textsuperscript{23} In cases where the anamnesis and physical symptoms are incorrectly interpreted, the imaging studies are likely to be misinterpreted as well. Because MRI may not be conclusive regarding the diagnosis in these cases, the main reason to make one prior to biopsy is to document the extension of the lesion in order to guide further treatment.\textsuperscript{25} Although a biopsy is indicated to rule out malignancies in cases where the diagnosis remains equivocal following history, physical examination, and imaging, sufficient expertise is required to differentiate between IH, other vascular anomalies, and a malignant vascular lesion.\textsuperscript{19,26,27}

**Diagnostic pitfalls in our seven cases**

In our study we found seven children with a malignancy. The initial diagnosis of IH, rather than malignancy, was incorrectly reached in these seven children at various stages of the diagnostic pathway of anamnesis, physical examination, and additional investigations (e.g. ultrasonography or MRI). Structured, thorough anamnesis and physical examination based on knowledge of the standard course of an IH would have led to the conclusion that these lesions could not have been IH. In two children (cases A and C), the age of onset (60, respectively 20 months) had not been consistent with that of an IH (Table 4).

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at onset</th>
<th>Physical symptoms</th>
<th>Ultrasonography</th>
<th>MRI</th>
</tr>
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<tbody>
<tr>
<td>A</td>
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<td>B</td>
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<td>D</td>
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<td>n.a.</td>
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<td>E</td>
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<td>+</td>
<td>+</td>
<td>+/-</td>
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<tr>
<td>F</td>
<td>+</td>
<td>+</td>
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<tr>
<td>G</td>
<td>--</td>
<td>+</td>
<td>+/-</td>
<td>--</td>
</tr>
</tbody>
</table>

n.a.: not applicable; +/-: inconclusive examination

*: consistent with vascular malformation
In three children (cases D, E and G), the anomaly was full-grown at birth and not persistent with one of the minor skin precursors of IH. In two children (cases A and B), the lack of proliferation phase did not agree with this diagnosis. In the one remaining child (case F), the anomaly did mimic an IH, but long-standing ulceration and the firmness of the tumor raised the suspicion of our team.

When anamnesis and physical examination are inconclusive, additional investigations may offer complementary information. Except for pathological examination of biopsies, however, these proved not to have helped to reach the definitive diagnosis in our series.

We conclude that early age malignant tumors can mimic benign IH and add two malignancies to the differential diagnosis of IH. Additional steps toward a definitive diagnosis must be taken in cases where the course of an anomaly that looks like an IH does not fit the standard clinically course of an IH. In cases where a malignancy cannot be ruled out, a biopsy needs to be examined by a pathologist who is experienced in vascular anomalies.
Chapter 5

Reference List

Malignant differential diagnosis in children referred for infantile hemangioma


