Angiogenesis in congenital vascular malformations: a dynamic view on a static lesion

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Chapter 1

General Introduction
Case report
A male patient, who came to our hospital at the age of 40, was known since birth with a reddish discoloration of his right cheek and below his right orbit. The lesion slowly increased in size over time. At the age of 12 a diagnosis congenital vascular malformation was made based on clinical and angiographic investigations (Figure 1A). And, due to the rapid filling phase of the venous component of the lesion during angiography at that time, which indicates the presence of arteriovenous (AV)-fistulas in the lesion, the malformation appeared to be of the arteriovenous type. At the age of 40 he noticed sudden onset massive enlargement of the lesion which developed in a period of 3-4 weeks time (Figure 1B). This eventually resulted in loss of vision on the right side. Histopathology of the mass revealed the well-known features of an arteriovenous malformation, being conglomerates of malformed arteries and veins. But in addition to these findings, there was an unexpected extensive solid proliferation of benign, but immature microvessels, which filled up the extravascular spaces of the malformation, indicating microvascular angiogenesis in the vascular malformation.

Considering the widely accepted congenital nature of vascular malformations, this notion of such a massive angiogenic response was of great interest, but at the same time a lot of questions came up. Congenital vascular malformations are mass-forming lesions, mostly quiescent, which usually progress only slowly and grow commensurately with life. It is known that malformations can become symptomatic because of episodes of sudden growth, which is usually explained by secondary

Figure 1. A. The patient at the age of 12 with discoloration of his right orbit and cheek (arrows) due to an underlying arteriovenous malformation. B. The same patient at the age of 40, showing expansion of the lesion. (published with permission of the patient).
complications, such as inflammation, thrombosis, dilatation and arterialization of veins. This occurs in most cases during pregnancy, puberty and also trauma. The finding of proliferating microvessels as an explanation for the sudden growth of the lesion has thus far been described only anecdotally. What exactly is the cause of such a microvascular response? Is it part of the vascular malformation or should it be considered as secondary event in response to situations of hypoxia, inflammation or else? Is this proliferative angiogenesis a common phenomenon in vascular malformations and are those findings seen in all different types of vascular malformations? Is it a site-specific complication? Is there a special trigger that makes a vascular malformation form new capillaries? Can it be distinguished from vasoproliferation in other vascular lesions? Is this proliferative angiogenesis a solitary event in these lesions? Is there an association in vascular malformations with an increase in other components, for example nerves, since vessels and nerves are also developmentally closely related?
These questions form the basis of the investigations that are described in this thesis.

Outline of the thesis

Part I  Vascular lesions and angiogenesis – an overview
The principal areas of interest of this thesis relate to vascular malformations on the one hand and angiogenesis on the other hand. Chapter 2 gives an overview of the current insights in the pathology of vascular malformations in skin and soft tissue in children and adolescence, particularly their classification and differential diagnosis towards other vascular lesions. In Chapter 3, general aspects of angiogenesis as far as they are relevant for the growth of benign vascular lesions are reviewed.

Part II  Angiogenesis in vascular malformations
In Chapter 4 the occurrence and extent of proliferative angiogenesis is investigated in a large series of surgically treated vascular malformations, and evaluated in relation to various clinical parameters, like age, sex and topographic location. Benign vascular anomalies represent different entities with distinct clinical appearances, and many of them have a biphasic course of proliferative growth of microvessels followed by vascular maturation. In Chapter 5 we investigated whether the observed microvascular growth in malformations also follows such a pattern of maturation, because this could provide a clue to its nature. We compared the immunomorphological features of vascular proliferation and maturation of vascular malformations with those of the most common types of vascular lesions, being infantile hemangiomas and pyogenic granulomas. These findings were related to in
situ expression of angiogenic factors and cell cycle dependent proteins. One of the key regulators in angiogenesis is vascular endothelial growth factor antibody (VEGF-A) and its presence and activity in angiogenic responses has been studied extensively in various pathological situations. We noticed that there is a wide array of commercially available monoclonal antibodies for VEGF-A, of which the reported specificity and staining patterns as reported in the literature are at least inconsistent or in some cases even contradictory. In Chapter 6 we compared nine commercially available VEGF antibodies for their ability to immunostain vascular malformations.

Vascular malformations are clinically categorized by their hemodynamic features as high (fast) or low (slow) flow. In Chapter 7 the relation between flow velocity and occurrence of proliferative angiogenesis is investigated in a large series of resected arteriovenous malformations, of which the flow patterns were assessed clinically before the surgical resection took place.

**Part III    Vascular malformations at specific topographic sites**
In Chapter 8 we investigated the pathology of facial vascular malformations that underlie a clinical manifestation of lip hypertrophy.
Chapter 9 describes the pathology of two cases of AVMs in the heart also complicated by the occurrence of proliferative angiogenesis.
In Chapter 10 cerebrovascular malformations were investigated for the presence of the glucose transporter protein GLUT1, which is expressed in endothelial cells of the brain microvasculature, but also used as an important immunomarker in the differential diagnosis of extracranial vascular lesions.

**Part IV    Nerves in vascular malformations**
In Chapter 11 and 12 the presence of an intralesional component of nerves in vascular malformations and their relationship with different types of vessels in the malformation is investigated.

**Part V    Discussion**
Chapter 13 and 14 provide the summary and discussion of this thesis in English and Dutch.