Case Report

Concurrent thalidomide and radiation therapy for extensive arterio-venous malformations

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We report on a patient with extensive cervical, thoracic and left arm arterio-venous malformations (AVM) who had extensive growth of the AVM after prior embolization and surgical ligation, and who responded dramatically after concurrent radiation and thalidomide therapy. His clinical course suggests that local up-regulation of angiogenesis plays an important role in the pathogenesis of AVM.

The patient is a 45-year-old male who first noted tortuous, dilated subcutaneous blood vessels in his neck and left shoulder regions during puberty. At age 34, an interventional radiologist embolized several of the abnormal arteries, but inadvertently occluded the left brachial artery, causing acute ischemia of the left upper extremity that required above-elbow amputation. After rapid growth of the AVM, the left subclavian artery was surgically ligated, only to result in extensive new AVM feeding from the vertebral artery. When the patient first came to our attention in May 2000, his resting cardiac output, measured by echocardiography, was markedly elevated to 16 l/min (normal range for a man of his size 4.9–7.9 l/min), and AVM were feeding from the left external carotid artery, both vertebral arteries and several intercostal arteries (Fig. 1). The patient bled profusely from the left arm stump whenever the bandage was changed, requiring ligation of the culprit vessel.

Following a multidisciplinary medical/radiological/surgical consultation, we concluded that embolization of the numerous feeding arteries (Fig. 1) was no longer feasible, and neither was complete surgical resection of the AVM. Since the patient was in danger of congestive heart failure, we resorted to regional radiotherapy with the aim of reducing the size of his AVM. In June/July 2000 the patient received a total dose of 45 Gy over four adjacent fields, covering the left side of his neck, clavicular region and left arm stump, avoiding as much as possible direct exposure of the lung. The ensuing radiation endarteritis and fibrosis reduced the volume of the abnormal vasculature in the irradiated regions and decreased the resting cardiac output to 7.4 – 9.7 l/min (transmitral and transaortic flows, respectively). Angiography still showed extensive AVM feeding from both vertebral arteries, occipital branches of the left external carotid artery and intercostal arteries, and in September 2003, the resting cardiac output had increased to 9.3 – 11.4 l/min. Since we hypothesized that each attempt of obliterating the AVM is accompanied by regional hypoxia which stimulates rebound growth of abnormal vasculature, we decided to combine a second round of radiation therapy with pharmacological inhibition of angiogenesis by thalidomide (Myrin®, Lipomed AG, Switzerland), an immunomodulatory drug with pronounced antiangiogenic activity (1, 2). After discussing the proposed treatment, its potential side effects and obligatory safety measures with our patient, who signed informed consent, thalidomide was started in December 2003, titrated to 300 mg/day and continued for one year without adverse effects such as excessive drowsiness, peripheral neuropathy, pronounced constipation or haematological abnormalities. Concomitantly, a second round of radiotherapy (20 Gy) was administered to the left shoulder and arm stump in January/February, 2004. Systemic plasma concentrations of basic fibroblast growth factor (b-FGF) and vascular endothelial growth factor (VEGF) were normal at baseline and during combined thalidomide-radiation treatment (Table 1). In June 2004, vascular ultrasound showed that several of the abnormal vessels in the irradiated area were obliterated. For almost two years after discontinuing thalidomide, the resting cardiac output remained at 7.4 l/min or less, although a substantial portion of the AVM was still patent. Our patient continues to work in computing and informatics, reports good exercise tolerance and enjoys hiking in the Alps.

Discussion

AVM arise from local defects in vascular morphogenesis. In a restricted area of the body, anatomically abnormal arteries and arterioles drain directly into venules without an intervening microcirculatory network (3). High blood flow through the low-resistance vascular bed can lead to congestive heart failure (3–6) and may cause significant bleeding (4–6). In contrast to hemangiomas, high-flow AVM are rare (3–6). The incidence of AVM in the brain has been estimated at 1 per 100,000 people and the prevalence at 18/100,000 adults (7), but there are no reliable epidemiological data on extracranial AVM. Incomplete treatment of AVM by embolization, ligation or partial resection often leads to rebound growth of the abnormal vasculature and worsening of symptoms if the AVM are "extratruncular", i.e. "derived from developmental arrest during early embryonic life" (4, 6).

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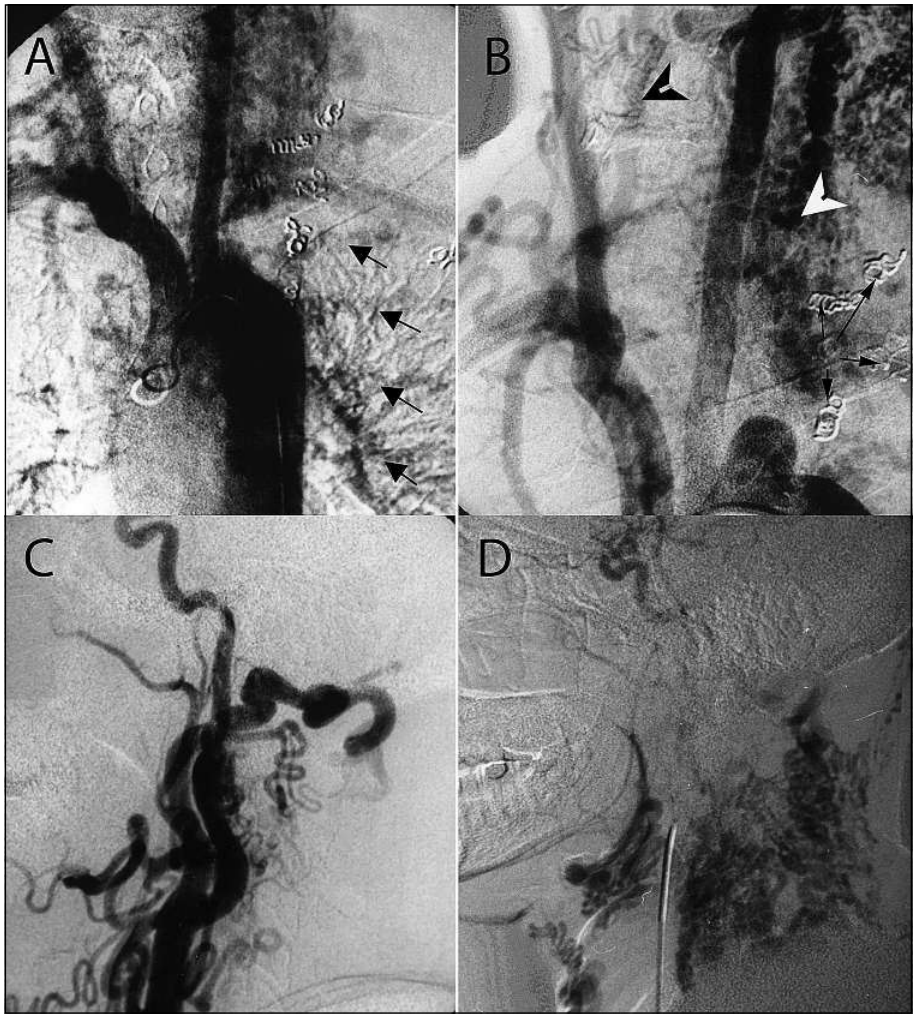

Figure 1: The extent of our patient's AVM in May 2000. A) Angiogram of the aortic arch showing the abnormal arteries feeding from the left external carotid artery, both vertebral arteries and several intercostal arteries (arrows), while the left subclavian artery had been ligated; B) extensive abnormal vasculature arising from the left vertebral and external carotid arteries (white arrowhead), less extensive abnormal vasculature arising from the right vertebral artery (black arrowhead), and embolization coils from a previous treatment attempt (arrows); C) early arterial phase of the left carotid angiogram showing abnormal arteries arising from the external carotid and its branches; D) late phase of the left carotid angiogram showing the extent of the cervical AVM.

Lee et al. describe a multidisciplinary approach to managing peripheral AVM with excellent overall results, consisting of accurate imaging diagnostics, embolo/sclerotherapy and tailored surgical procedures (4–6). However, lesions in the head and neck region – as in our patient – are less amenable to such treatment modalities (8). The multitude of feeding vessels of our patient's AVM, spread over the carotid, vertebral and thoracic aortic territories, precluded comprehensive embolo-sclerotherapy as well as complete surgical excision. Radiation therapy, albeit untested in peripheral AVM, was chosen as a palliative method of controlling the AVM and reducing the cardiac output. Stereotactic radiation therapy is the recommended treatment for AVM related to the central nervous system when microsurgery carries a high risk of morbidity (9, 10). Although radiation *per se* inhibits angiogenesis, which was demonstrated in a model of cerebral AVM tissue transplanted into rat corneas (11), this inhibition may not suffice in unfavorable conditions. Prior embolization of brain AVM paradoxically decreases the obliteration rate by subsequent radiation therapy (10), which is consistent with the hypothesis that tissue hypoxia following incomplete AVM obliteration stimulates angiogenesis and leads to rebound growth of the AVM. Angiogenesis in ischemic tissue is triggered by hypoxia-inducible factor (HIF) which activates numerous target genes, among them genes for vascular endothelial growth factor (VEGF) and its receptor VEGFR2 that stimulate proliferation of endothelial cells from existing vessels (12, 13). Angiogenesis is modulated by complex signaling of various chemokines (14, 15), some of which are inhibited by thalidomide (16). Arteriogenesis, the remodeling and enlargement of existing small vessels that enables increased blood flow, is primarily dependent on haemodynamic factors, but HIF-inducible endothelial nitric oxide synthase (eNOS), VEGFR1 and placental growth factor (PLGF) also play a role (12, 17). Therefore, when our patient's resting cardiac output slowly, but notably, increased after the first round

Table 1: Systemic plasma levels of basic fibroblast growth factor (b-FGF) and vascular endothelial growth factor (VEGF).

	Normal	Basline* (Dec-19–03)	During thalidomide treatment (Jan-8–04)	During thalidomide, following radiation (May-11–04)
b-FGF	<32 pg/ml	0.2	0.8	0
VEGF	<788 pg/ml	130	305	167

*Initial radiation therapy in April 2001.

of radiation, we decided to combine another round of radiation with pharmacological inhibition of angiogenesis. Among several different mechanisms of action, thalidomide inhibits expression of VEGF (2, 18). Thalidomide's antiangiogenic activity underlies its teratogenicity (1), but, on the other hand, in conjunction with its immunomodulatory effects, plays a role in its efficacy against various malignancies (2). Case reports have described successful use of thalidomide in treatment of severe intestinal bleeding related to angiodysplasias, hereditary hemorrhagic telangiectasia and even Crohn's disease (19–24). Thalidomide also increases the risk of venous thromboembolism (25, 26), and its use has been sporadically linked to arterial thrombosis (27, 28). Therefore, thalidomide's antiangiogenic and prothrombotic action could have been beneficial in obliterating our patient's AVM. Apart from thalidomide's teratogenicity resulting in focomelia, its most important side effects are drowsiness and fatigue, peripheral sensory neuropathy, orthostatic hypotension, constipation, neutropenia and prothrombotic effects, especially pronounced in patients with plasma cell dyscrasias (18, 25–29). Strict monitoring and adherence to safety measures are required during thalidomide treatment (18, 29).

The molecular mechanisms of AVM growth have not yet been fully elucidated. Although we did not detect increased systemic levels of pro-angiogenic factors VEGF and basic fibroblast growth factor (b-FGF) (Table), our patient's clinical course supports the hypothesis that AVM growth, especially the rebound expansion after partial treatment, results from locally hyperactive angiogenesis. It is possible that a local increase in VEGF and b-FGF was missed by sampling venous blood from the unaffected arm, but on the other hand our result is consistent with the proposed deficient down-regulation of angiogenesis in AVM, since endothelial cells from AVM do not respond to inhibitory cytokines such as interleukin-1β, tumor necrosis factor-α, transforming growth factor-β, and interferon-γ (3). The main limitation of our case report is the uncertainty whether the clinical success was related to thalidomide or only to the second round of radiation treatment.

In conclusion, this the first report demonstrating that a combination of radiotherapy and pharmacological antiangiogenic/immunomodulatory treatment provided prolonged relief to a patient with extensive extracranial AVM that were not amenable to complete embolization and radical surgery. This approach merits further assessment and investigation.

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