

Vascular malformation and their unpredictable evolution: A true challenge for physicians

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Summary. Vascular anomalies are mainly divided into two groups: vasoproliferative/vascular neoplasms (e.g., hemangioma), and vascular malformations (VMs). The main difference between the two resides in the histopathological assessment, while vascular tumors are true neoplasm, typically congenital with rapid postnatal growth, and eventual slow regression; VMs have a single endothelial cell lining, tend to be regarded as acquired despite being congenital in nature, can undergo sudden and massive growth, miming neoplastic proliferation. Arteriovenous malformation (AVMs) are one type of fast flow VMs, with a four-stage natural history, and potentially disruptive evolution. Magnetic resonance is the gold-standard for diagnosis and pre-operative planning while computer tomography is particularly valuable for AVMs involving bones, and selective angiography can define source / draining vessels for sclerotherapy and surgical planning. Given their unpredictable evolution, AVMs shouldn't be treated until symptomatic, complicated, or aesthetically unacceptable. Surgical resection should be preceded by arterial embolization from 24 to 72 hours, which must be extensive in order to reduce the risk of recurrence. Pain due to ischemic condition is one of the most common and debilitating symptoms of AVM, while gassosus gangrene is the most feared complication as they can become pabulum for bacteria overgrowth eventually resulting in necrotizing fasciitis. Given their clinical evolution, VMs pose physicians at great challenge in identifying the best-suited treatment for each case. It is of paramount importance to be able to make accurate diagnosis, understand the basic physiology, and use appropriate diagnostic and treatment modalities to optimize outcome. Proper multidisciplinary approach along with constant psychological support is the basis for a successful final outcome. Aim of this work was to provide a deeper insight into these relatively uncommon pathology and related hardship that afflicts both patients and their families. (www.actabiomedica.it)

Key words: vascular malformation, arteriovenous malformation, surgical management, clinical management, hand surgery

Background and aim of the work

Vascular malformations are challenging for physicians both at identification and treatment given their different etiology and unpredictable evolution.

The aim of this work was to provide a deeper insight into these relatively uncommon pathology and related hardship that afflicts both patients and their families.

The term vascular malformation comprises a wide range of vascular-related development disorders (1).

Among the various classification system proposed, the one described by Mulliken and established by the International Society for the Study of Vascular Anomalies (ISSVA) is the most widely accepted. It divides vascular anomalies mainly into two groups: vasoproliferative/vascular neoplasms (e.g., hemangioma), and vascular malformations (VMs) (2).

The main difference between the two resides in the histopathological assessment, where vascular tumors are true neoplasm characterized by and increased and pathologic vascular cell proliferation. These are the

most frequent benign tumors that occur in the childhood (8-12% prevalence rate). They are typically congenital with rapid postnatal growth, while they eventually slowly regress during late childhood (3).

Conversely VMs have a single endothelial cell lining (4). VMs tend to be regarded as acquired despite being congenital in nature. Indeed, they are usually unrecognized at birth, and undergo progressive growth following patient's one, thus coming into clinical evidence only during late adolescence or early adulthood. Nevertheless, VMs can undergo sudden and massive growth, miming neoplastic proliferation (1).

VMs represent 2-6% of all upper extremity neoplasms, having the same incidence between males and females; all segments of the upper limb can be affected, whereas hand is the most frequent one, being surpassed by head & neck district only in incidence (5). VMs tend to be isolated lesions; nevertheless they can be one of the manifestations of rare syndromes (e.g., Maffucci syndrome, Proteus syndrome) (6, 7).

Classification

VMs can be mainly subdivided by their flow characteristic into slow-flow and fast-flow (1).

Capillary (CM), lymphatic (LM), and venous (VM) malformations are slow-flow VM, while arterial (AM) and arteriovenous (AVM) ones are fast-flow. Complex malformation (e.g., limphovenous and capillarolymphatic malformations) can also be seen. Among the various proposed classification systems for AVM, none of them referred to the accompanying clinical findings that usually guide the treatment (8, 9).

Histopathological findings

Each VM subgroup has peculiar histopathologic features with a common a single endothelial cell lining (10).

AVMs develop from an identified source vessel ("nidus") which shunt arterial flow into the venous system and usually consist of arterial feeders, micro- and macro arteriovenous fistulas, and ecstatic veins (11).

Thickened fibromuscular walls, fragmented elastic lamina, disorganized middle muscular layer, and fibrotic stroma characterize arterial segments of AVMs. Venous segments in immature AVMs are "arterialized" because they present with reactive muscular hyperplasia that eventually turn into degenerative fibrosis and muscular atrophy in a mature AVM (12).

Diagnosis

Careful clinical exam is usually enough for correct diagnosis (1). CMs are red, plane angiomatous lesions that do not change with time, LMs never regress yet expand and contract based on the amount of lymphatic fluid present and the presence of bleeding or inflammation (13). VMs are bluish, soft, compressible lesions that are not translucent to direct light and are enlarged in declivous area.

AVMs are slightly compressible, pulsatile with a palpable thrill, and are characterized by increased local temperature (1). Present at birth, their bluish color can be confused with hemangioma or port-wine strains. They can affect bone and soft tissue with no history of pain, but rather intermittent bleeding (14). Local trauma and hormonal changes (e.g., puberty, pregnancy, hormonal therapies) may act as expansion triggers. Body segments affected by AVMs tend to undergo hypertrophic growth due to the increased blood flow. As a result, bone fractures can occur given the faster bone growth. When AVMs have visceral or mucosal localization, bleeding episodes can be fatal. Furthermore, massive AVMs can provoke perturbation of the cardiac function. AVMs have a four-stage natural history described by Schobinger (12): quiescence, expansion, destruction, decompensation.

Even though ultrasound (US) and color Doppler are entry-level exams that can help in demonstrating arterial output and determine AVMs expansion in time; magnetic resonance (MR) is the gold-standard to precisely determine the extent of the lesion for operative planning (15). Computer tomography (CT) is particularly valuable for AVMs of bones, while selective angiography can define source / draining vessels, and is used only for sclerotherapy and surgical planning (16).

Treatment

Surgical approach

AVMs shouldn't be treated until symptomatic (ischemic pain), complicated (recalcitrant ulceration, bleeding, increased cardiac output), or aesthetically unacceptable (17).

Sclerotherapy or direct embolization of the nidus is still a matter of debate at early stage, while feeding vessels should never be ligated since it will cause rapid recruitment of nearby collaterals to supply the nidus, hence increasing final blood flow. Nevertheless, arterial embolization should be done 24 to 72 hours prior to surgical resection to reduce the risk for intraoperative bleeding (18). Furthermore super-selective arterial embolization can be used as temporary solution for ischemic pain, bleeding, and cardiac failure. Serial super-selective arterial embolization can also be performed starting from peripheral vessels as alternative to surgical resection when not feasible (19).

Arterial embolization does not reduce the extent of surgical resection, which must be extensive in order to reduce the risk of recurrence. Indeed, recurrence rates are extremely high when complete surgical removal cannot be performed (20). Therefore the combined approach of arterial embolization followed by surgical removal has the highest success rate (21). Overlying skin can be saved only when macroscopically not involved. Nevertheless, resections tend to leave large defects, which may be covered with microsurgical free flaps. Thus, surgical resection should be done only after careful cost-benefit analysis. AVMs only rarely do not relapse; hence a strict clinical and radiological follow-up program should be observed for years.

For what specifically concerns AVM selectively localized to the hand, Al-Quattan et al. (22) proposed a new classification system and a related treatment algorithm.

Medical support

Pain due to ischemic condition is one of the most common and debilitating symptoms of AVM (23). Painkillers are usually not enough to control it, and morphine-derived analgesics are usually required.

Gangrene is the most feared complication of AVM (24). Indeed, ischemic lesions can become a pabulum for bacterial overgrowth. Drainage of the suppurative tissue and proper antibiotic therapy are the two main strategies for patients' salvage.

Furthermore, superficial wounds consequence of spontaneous bleeding can become infected in 30% of cases by *Clostridium*, eventually resulting in necrotizing fasciitis.

Necrotizing fasciitis can occur in 0.4 out of 100,000 people in the adult population, 0.08 out of 100,000 in the childhood (25). Unfortunately, it can bring to death in 43-73% of the cases, varying on the basis of age, nutritional status, comorbidities, and general condition.

Again, early diagnosis, along with surgical drainage and proper antibiotic treatment are the only life-saving procedures available (25).

When occurring to the forearm and to the fingers, necrotizing fasciitis can cause a compartmental syndrome that requires immediate decompression by means of fasciotomy and adequate drainage of suppurative collection (25).

Antibiotic therapy of choice is oxycillin alternative to ampicillin/sulbactam. Vancomycin, clindamycin, cotrimoxazole, fluorochinolons, are usually employed in case of penicillin allergy or serious infections. Macrolids are commonly administered only in mild infections. Patients affected by diabetes mellitus are more prone to infections caused by *Enterobacteriaceae*, hence third generation cephalosporin or ampicillin/sulbactam are administered along with an aminoglycoside.

Case report

The first time M.S. came at our Department, she was a 21-year old female patient that had her left clavicle broken during her delivery. Her left arm appeared bigger and darker in color than the contralateral one since early age. When she was 4-year old, she underwent an arteriography, which demonstrated the presence of an AVM affecting the proximal third of the left humerus where a muscular perforator of the omeral artery was directly connected to the left omeral vein with no interposing capillary network. Furthermore, an Rx

showed initial sign of omeral bone erosion. Selective arterial embolization was then performed. When she was 7-year old, a second super-selective arterial embolization was performed, and bone-cement was implanted in the omeral bone to prevent spontaneous rupture. She was diagnosed with Albright syndrome when at 11-year old a CT scan demonstrated fibrous dysplasia of both femours and left tibial bone. Hand involvement became evident when she was 12-year old: she complained of pain at the left 5th digit and ulnar edge of forearm along with fever (Figure 1). In the following three years, she was subjected to serial selective arterial embolization. When she was 17-year old, selective arterial embolization of two massive fistulas at the level of the elbow was performed and was complicated by left cephalic vein thrombophlebitis. The following year, severe fever, swelling and pain to the left upper limb were symptoms of bacterial dermoipodermatitis, followed by septic shock and massive hemorrhage coming from the dorsum of the left hand (Figure 2). Applying a compressing garment left in place for two months stopped hemorrhage, and proper antibiotic administration plus resuscitation measures were able to prevent septic shock from creating further complications. The resulting wound was left to heal for secondary intention with a resulting retracting scar (Figure 3). During the following three years numerous lymphatic fistulas and infections occurred at her left upper limb, furthermore her forth left-hand digit had to be amputated. Eventually we lost the patients during follow-up (Figure 4).

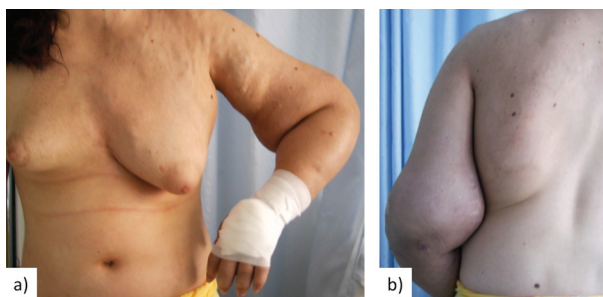


Figure 2. When the patient was 18-year old she presented with severe fever, swelling and pain to the left upper limb as consequence of bacterial dermoipodermatitis, followed by septic shock and massive hemorrhage coming from the dorsum of the left hand. a) Applying a compressing garment left in place for two months stopped hemorrhage, and proper antibiotic administration plus resuscitation measures were able to prevent septic shock from creating further complications. b) Note the massive swelling at the level of the elbow due to the arteriovenous malformation that relapsed after numerous selective arterial embolization

Conclusions

VMs have a subtle behavior, being unrecognized or silent for most of patient's lifetime and unmasking themselves anytime with no putative cause recognizable and with unpredictable evolution. Given their clinical evolution, VMs pose physicians at great challenge in identifying the best-suited treatment for each case. It is of paramount importance to be able to make accurate diagnosis, understand the basic physiology, and use appropriate diagnostic and treatment modalities

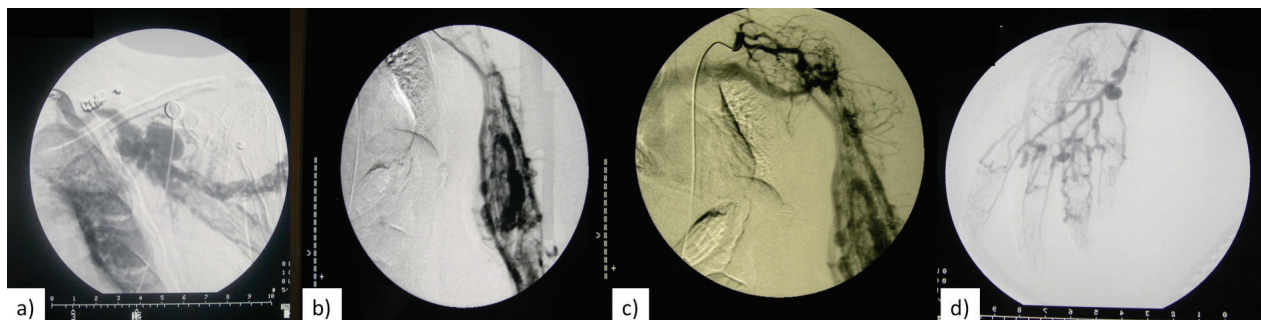


Figure 1. These angiograms performed when the patient was 12-year old show: a) the proximal humeral arteriovenous malformation that already underwent two selective embolization, b) - c) two massive arteriovenous malformations at the level of the elbow; d) the initial involvement of the left hand with poor distal vascularization to the fingers



Figure 3. a) - b) The compressing garment applied to stop the massive hemorrhage coming from the dorsum of the left hand was left in place for two months. c) - d) Once removed the resulted wound was left to heal by secondary intention with a resulting contracting scar



Figure 4. a) - b) When the patient was 21-year old she presented with pain to the 4th finger of the left hand and a necrotizing wound at the level of the dorsal proximal interphalangeal joint that required its amputation. c) - d) The radiographs performed in that occasion showed the extensive erosions to the bone of the hand starting from the middle shaft of the metacarpal bone.

to optimize outcome. Furthermore, it is important to make patients and their parents understand that they have to be regularly followed by specialized center in order to identify any complication or evolution at early stage when they are more likely to be treatable. Proper multidisciplinary approach along with constant psychological support are the basis for a successful final outcome.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Furthermore for this type of study formal consent is not required.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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