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Effects of Electrochemotherapy in Treating Patients with Venous Malformations

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Background: Treatment of venous malformations poses a major clinical challenge for the contemporary medicine. Surgical resection is difficult and frequently unsuccessful, radiological intervention with embolization has an ill-defined role, and conventional sclerotherapy has little to offer for a large scale disease.
Objective: To evaluate the efficacy and safety of electrochemotherapy in treating venous malformations.
Methods: Electrochemotherapy was applied on 665 patients with venous malformations of limbs and trunk and 505 cases were followed up for half to 6 years. There were 228 males and 277 females, aged 2-59 years and 17.5 years on average. Diagnosis was made by clinical manifestations, ultrasonic examination and/or magnetic resonance imaging. Inserting the platinum electrodes into tumor through a trocar with plastic insulating cannula percutaneously and connecting the electrodes with the electrochemical therapeutic apparatus in anodes and cathodes separately. Then electricity was given. The treating voltage is 6-12V and volume 100-180mA, the total electricity used is in general 80-100 coulombs per 1.0 square centimeter of tumors' area.
Results: The primary efficacy end point was defined as an improvement of patients' symptoms and a reduction in size of tumor 6 months after completion of the treatment. Clinical results were graded as follows: Grade 1, clinical obliteration, functional impairment of the diseased limbs recover to normal and the tumor decreases over 75%; Grade 2, most clinical symptoms disappear and functional impairment of the diseased limbs improve significantly, the tumor decreases 50-70%; Grade 3, clinical symptoms and functional impairment of the diseased limbs improve, the tumor decreases 25-50%; Grade 4, poor, little or no improvement of symptoms and functional impairment of the diseased limbs, the tumor decreases less 25%. The efficacy in 152 (30.1%) patients was classified as grade 1, 234 (46.3%) as grade 2, 96 (19.0%) as grade 3 and 23 (4.6%) as grade 4. The total efficacy was 95.4%.
Conclusion: Electrochemotherapy shows special superiorities in treating venous malformations, it is proved to bring a confirmed clinical efficacy、less injury、quick recovery、being simple in operation and less complications.
Key words: venous malformations; electrochemotherapy; clinical effect

Treatment of venous malformations (VMs) poses a major clinical challenge for the contemporary medicine. The traditional surgical resection is difficult and frequently unsuccessful, it remains the shortcomings of huge injury, much complications, high recurrence rate and leaves operative scar or limbs disturbance. Radiological intervention with embolization has an ill-defined role, and conventional sclerotherapy has little to offer for a large scale disease. The treatment of 665 patients with VMs of limbs and trunk (followed up 505 cases) by electrochemotherapy (EChT) has shown a favourable clinical effect. It was reviewed and summed up retrospectively, and reported as follows.

Methods

Clinical materials

Evaluate retrospectively 665 patients with VMs of limbs and trunk been treated by EChT from Jan. 2000 to July.2009 in our department and 505 cases were followed up for half to 6 years. They were 228 males and 277 females, aged 2-59 years, 17.5 years on average. The diagnosis of VMs was made

by clinical manifestations, ultrasonic examination and/or magnetic resonance imaging (MRI). There was no abnormality when the patients were born in most cases. There would appear a local swelling tumour or become bigger diameter of the diseased limb than the health one as the patients growing up. Most of the patients had distending feeling and pain after exercise, some of them might have diseased limbs disturbance. Physical examination might find diseased area having a swelling tumour or bigger diameter than the health one. There might appear concave edema in the diseased limbs, usually after the patient has a long time standing. Most of the patients had normal colour of skin and some of them might have madder red or an irregular tumour. Part of the patients had functional impairment of the diseased limbs. Some patients with huge vascular malformation might concomitant with thrombocytopenia. There might appear abnormal signal shadow and evident blood flow signal in diseased region by color echograpy. MRI could confirm the diseased region, normal or low signal in T1W and high signal in T2W press fat imaging. There were 268 cases (53.1%) in our group were recurrent patients after surgical resection. Table 1. and Table 2. show the distribution and size of the tumors in total 505 cases.

Diseased region	Up limbs	Lower limbs	Trunk	Total
No. (%)	102 (20.2)	313 (62.0)	90 (17.8)	505

Table 1. The tumor distribution in 505 cases

Diameter（cm）	< 10	11-20	21-30	>30
No.（%）	36 (7.1)	59 (11.7)	258 (51.1)	152 (30.1)

Table 2. The tumor size in 505 cases（Diameter cm）

Treatment facility

The electrochemical therapeutic instrument type ZAY-B and platinum needles used were manufactured by Beijing Weiliheng Scientific and Technologic Development Co. Ltd. Beijing, P. R. China. The diameter of platinum needles is 0.7mm and its length 150mm. (see Figure 1.)

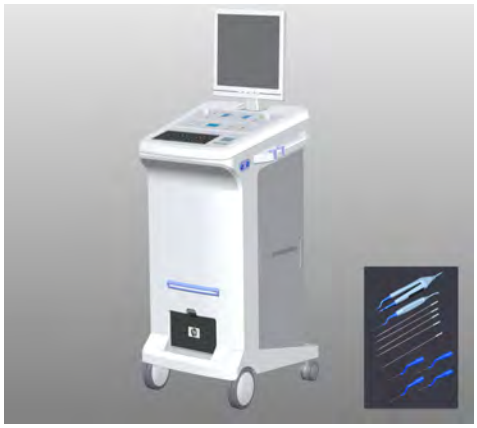


Figure 1. The electrochemical therapeutic instrument type ZAY-B and platinum needles

Treatment Methods

Blood coagulated function、ECG、chest X-Ray、hepatic and renal function of the patients be tested before operation. The anaesthetic approach was selected according to the location and size of the tumor. Brachial plexus anaesthesia or spinal anaesthesia was applied for limbs disease in adult patients. General anaesthesia through tracheal intubation was applied for others. Operating field was sterilized with iodophor and covered by sterilized sheet. Confirming the diseased region and scope by MRI or echography, 18G trocar was used to insert into diseased region from 2cm beyond the margin of tumor depending on the size and shape of it, usually along Y direction of the tumor. It is show that

the trocar is in correct position when blood flow is seen in the end of trocar. Pulling out the needle core of trocar and inserting the electrode into diseased region through the trocar. Pay attention to place the needles cover whole disease area. The number of needle inserted was estimated according to the shape and size of tumor, they were allocated so as to cover the whole tumor with a space of 1-1.5cm between one another, because the effective treating radius of each needle is 1.0cm, and the ratio between anode and cathode used was 1:1. The electrodes could be managed monolayer or multilayer according to the size of diseased region. The plastic insulating cannula was drawn out of the tumor to protect the normal tissue. The electrodes were connected to anodes and cathodes of electrochemical therapeutic instrument respectively. The electricity was then set up to begin the EChT with the current of 100-180mA and the voltage of 6-12V. The total electricity used was in general 80 100 couluns per 1cm diseased tissue.

The therapeutic voltage should be elevated from small to large gradually. The tumour might be changed from soft to hard by palpable during treatment. To turn down the voltage to zero than turn off the device when the therapy was completed. Electrodes and trocars were pulled out and gauze was used to press the needle hole of skin to stop bleeding. The operator might press diseased region by hand during operation, which could extrude the blood from the tumor, decrease the blood clot forming and increase the therapeutic effect by making closer contact of electrodes and tumors, all of that is attribute to quicker absorption of blood clot and necrotic tissues after operation. Bleomycin 8-16mg and dexamethasone 5mg was injacted into tumors percutaneously according to the size of tumor at the end of therapy.Antibiotics were used 1 day intravenously after EChT and the mean hospitalized time is 3-5 days.

Evaluation of therapeutic effect

It need 6 months or so to absorb for local necrotic tissues and coagulated clot after EChT, so the evaluation of therapeutic effect of EChT was made usually 6 months after treatment. The therapeutic effect was divided into 4 grades according to clinical follow up、echographic examination or MRI test for the change of improvement of patients' symptoms and reduction in size of tumor. Grade 1, clinical obliteration, functional impairment of the diseased limbs recover to normal and the tumor decreases over 75%; Grade 2, most clinical symptoms disappear and/or functional impairment of the diseased limbs improve significantly, the tumor decreases 50-75%; Grade 3, clinical symptoms and functional impairment of the diseased limbs improve, the tumor decreases 25-50%; Grade 4, poor, little or no improvement of symptoms and functional impairment of the diseased limbs, the tumor decreases less 25%.

Results

160 cases of 665 treated patients were lost follow up, remained 505 cases were followed up half to 6 years. One to three times EChT was performed. The final result was grade 1 152 cases (30.1%), grade 2 234 cases (46.3%), grade 3 96 cases (19.0%) and grade 4 23 cases (4.6%). The final effective rate was 95.4%. Table 3. and Table 4.

Region / Efficacy	Up limbs 102 (20.2%)	Lower limbs 313 (62%)	Trunk 90 (17.8%)	Total 505
Grade1 (%)	28 (27.4%)	93 (29.7%)	31 (34.4%)	152 (30.1%)
Grade 2 (%)	37 (36.3%)	154 (49.2%)	43 (47.8%)	234 (46.3%)
Grade 3 (%)	31 (30.4%)	51 (16.3%)	14 (15.6%)	96 (19.0%)
Grade 4 (%)	6 (5.8%)	15 (4.8%)	2 (2.2%)	23 (4.6%)
Effective rate (%)	96/102 94.1%)	298/313 (95.2%)	88/90 (97.8%)	482/505 (95.4%)

Table 3. The relationship between therapeutic effect and diseased region

Tumor diameter（cm）		< 10	11-20	21-30	> 30	Total
No.		36(7.1%)	59(11.7%)	258(51.1%)	152(30.1%)	505
Therapeutic effect（%）	Grade 1	22 (61.1%)	31 (52.5%)	70 (27.1%)	29 (19.1%)	152 （30.1%）
	Grade 2	12 (33.3%)	21 (35.6%)	140 (54.3%)	61 (40.1%)	234 （46.3%）
	Grade 3	2 (5.6%)	5 (8.5%)	41 (15.9%)	48 (31.6%)	96 （19.0%）
	Grade 4	0	2 (3.4%)	7 (2.7%)	14 (9.2%)	23 （4.6%）
	Effective rate	36/36(100%)	57/(96.6%)	251/258(97.3%)	138/152(90.8%)	482/505(95.4%)

Table 4. The relationship between therapeutic effect and tumor size

There were 14 (2.8%) cases of our group had recurrence in clinical manifestations after 1 to 2 years treated by EChT, MRI showed that the tumor size increased less 20%, clinical manifestations had got controlled by repeat EChT management.

The swelling in local area treated by EChT might be seen, it is usually fade away within 5-7 days. Parts of patients might have fever which usually was lower 38 . The complications of therapy include: 38 cases (7.5%) has skin burn in treating area, it could be healing by themselves; 15 cases (3.0%) have motor nerve of limbs injury, of them, 2 cases of radial and tibial nerve injury remained permanent and others recovered within 6 months; 5 cases has infection in deep part of wound and were healed by local incision and drainage with change dressings.

Discussion

Vascular malformatins is a group of congenital diseases caused by primitive angiodysplasia in the process of embryonic development. The definition of vascular anomalies is that the process is benign and that the tissue contains an increased number of normal or abnormal appearing vessels. Those clinical manifestations are different. The Venous malformations (VMs) is one of tough problems for contemporary medicine. Despite their benign nature, they can cause significant morbidity and even mortality if not properly recognized and treated. [1] [2]

Kransdorf found that approximately 30 % were vascular in a review of more than 900 benign and malignant soft tissue tumors diagnosed in the first 2 decades of life, [3] and in the United States, 40,000 children are born with vascular anomalies every year [4] However, our understanding of vascular anomalies has been often confusing. The old classifications were descriptive, extensive, and too complicated to be universally accepted and used. The word “hemangioma” was a generic term commonly employed for any kind of vascular tumor. [5]

In 1982, Mulliken and Glowacki introduced a classification scheme based on the clinical and histological characteristics of the lesion, they divided traditional hemangioma into hemangioma and vascular malformations. Hemangioma possesses proliferation of vascular endothelial cell in histology and vascular malformation dose not possess proliferation of vascular endothelial cell in histology, [6] see Table 5.

Hemangioma	Malformation
Proliferating phase	Capillary
Involuting phase	Venous
	Arterial
	Lymphatic
	Fistulae

Table 5. Classification of Vascular Lesions

They characterizes hemangiomas as having a rapid proliferative phase to a stable plateau phase followed by an involution phase, endothelial hyperplasia and an increased number of mast cells during the proliferative phase; and a normal mast cell count of the involutive phase. This differs from a vascular malformation, which displays a nonproliferative, mature endothelium and a normal mast cell population, and never involution spontaneously. This classification system has been widely accepted for its ease of use in clinical practice. However, it does not address the vascular dynamics of the lesion: ie, high flow versus low flow. Therefore, in 1993, Jackson et al. proposed a newer clinical classification system to assist in the selection of appropriate treatment, **[5]** see Table 6

I. Hemangioma
II. Vascular malformation
a. Low-flow lesion (venous malformation)
b. High-flow lesion (arteriovenous malformation)
III. Lymphatic malformation (lymphovenous malformation)

Table 6. Modified classification scheme of vascular anomalies

Hemangiomas are the most common tumors of infancy and are present in about 2% of neonates and become apparent in up to 10% in children by the age of 1 year. [7] They are seen in up to 23% of preterm infants weighing less than 1000 g. [8] Hemangiomas occur as an isolated lesion in 80% of cases, whereas the remaining 20% have two or more. There is a significant female predominance. The female-male ratio is approximately 1:3. **[5] [6]** [9] Hemangiomas are usually not present at birth and approximately 70-90% appear within one month. A rapid proliferative phase occurs during the first 9 to 12 months of life; this is followed by an involution phase that may be completed by 5 to 7 years of age, but can last up to 12 years. **[5]** [10] It has been estimated that involution usually occurs at a rate of 10% a year. It means that by 5 years of age, 50% have achieved complete involution and 70% by 7 years of age. The earlier the hemangioma involutes, the more complete is the involution. [11]

Vascular malformations have a lower incidence of occurrence than hemangiomas. However, they cause more clinical problems and are more frequently a source of severe cosmetic distress. **[5]** Although present at birth, they are occasionally not evident until later in life, in part due to a very slow flow with gradual venous pooling and dilation. The peak incidence of VMs is during the first 5 years of life, with 85% of patients diagnosed at this age. Histologically they appear as thin-walled vascular channels without smooth muscle, but with normal endothelial characteristics. Vascular malformations might be constituted by capillary、vein、artery or lymphatic vessel alone, it might be mixing constituted by more than two components also. Unlike hemangiomas, VMs grow proportionally to the size of the child, do not exhibit proliferation and any tendency involution spontaneously. They are normal in histology, but with abnormal architecture and continue to grow throughout life by slow expansion. There is no significant sex predominance and the female-male ratio is approximately 1:1. [11] [12] [13]

Venous malformations generally grow commensurately with the child and often expand in adulthood; however they are known to be hormonally modulated (i.e., exacerbated by puberty, menses, pregnancy, or antiovulant medication), trauma, including incomplete surgical resection also accelerate the expansion. A spontaneous enlargement secondary to thrombosis, ectasia, or development of new arteriovenous communications may occur in response to the upper factors. Extensive lesions can

cause consumptive coagulopathy. **[5]** [14] [15] Its can involve any structure in the body, including skin, mucosa, muscle, brain, bone, and visceral structures. [16] VMs of skeletal muscle represent a group of benign yet locally aggressive tumors. It is one of the most common deep-seated soft tissue tumors and the most common benign tumor in muscle. [17]

The most common type of vascular anomaly is the venous malformation. **[11]** Venous lesions were not considered to be familial; however, there is mounting evidence that they can be inherited in a mendelian fashion. [18] The influence for the human body by venous malformations includes: soreness or complaint in diseased area、the tumor compress and infiltrate the adjacent tissue、hindering the correlated limb's function、internal and external hemorrhage of the diseased area、patients' feature damage and some huge tumors might arouse coagulated disorders of patients **[18]**, [19] These venous lesions may become more pronounced with increased physical activity and during a Valsalva maneuver. Examination will reveal a compressible lesion that will refill upon release. **[7]** Pain striking in the morning or with overexertion is frequent due to blood stasis, congestion and microthrombi present within the lesion. Local swelling and pain are usually the main complaints of the patients although many venous malformations are asymptomatic. Expansion with dependant positioning and easy compressibility are unique findings with VMs **[11]** Cavernous hemangioma in traditional sense belongs to venous malformation, racemosum hemangioma belongs to arteriovenous malformation. Intramuscular vascular malformation might involve any muscle group of human body, for those that happened in trunk and limbs, lower limbs is the most common seen especially in thigh. **[19]**, [20]

The two noninvasive imaging techniques most often used in the examination of vascular anomalies are magnetic resonance imaging (MRI) and ultrasonography. The primary goals of imaging are to characterize the lesion, to determine the anatomic extent of the lesion, and to determine which tissues and adjacent vital structures are involved. [21] Magnetic resonance imaging is the most informative radiological technique for venous malformations, which are typically seen as normal or low signal in T1-weighted and high signal in fat-saturated T2-weighted. [22] Sonography has been useful in evaluating soft tissue masses suggestive of hemangiomas and vascular malformations, and the Doppler characteristics of vascular malformations are helpful in differentiating low-flow from high-flow lesions. Such lesions can usually be diagnosed without biopsy by careful history and physical examination techniques aided by imaging such as ultrasonography and MRI. **[21]** [23]

The definitive treatment of venous malformations is one of the most controversial topic in the medical practice, and as particularity of the disease, it also has been an obstinate disease for modern medicine. [24] The best treatment for venous malformations is unclear in part because the outcome is variable. The common therapeutic modalities include elastic compression garments, sclerosing agents, and surgical resection. [25], [26] Elevation of the affected area during sleep, compression garments, and aspirin can be important in limiting growth of the lesion as well as for symptomatic improvement. **[7]**

Intralesional sclerosants remains a mainstay in the contemporary management of venous malformations. Sclerosants damage the endothelial cells, resulting in intravascular thrombosis and fibrosis. The most common used sclerosants include absolute ethanol (95%–98%), bleomycin, sodium tetradecyl sulfate, carbonylamines, adrenocortical hormone, et. al. [27] **[2]** But sclerotherapy can require repeated treatments to maintain control of the lesion and usually is not considered curative as the lesion may eventually reexpand. In the literature control rates can be as high as 75%, but it may be more accurate to speak in terms of improvement, which approaches 100% in some series [28]

Another mainstay of therapy for venous malformations remains complete surgical extirpation but it is often not possible except for small, well-localized disease or the muscles which involved are

expendable. **[15]** However, the surgical treatment of more extensive lesions can often lead to massive bleeding, nerve damage, loss of motor function, cutaneous scarring and disfiguring. **[24]** There are only a few reports on the surgical treatment of these lesions, likely because the lesions may be difficult to remove due to their high vascularity, location of proximity to neurovascular structures, a tendency to infiltrate into the muscle and other tissues and a quite high of the recurrence rate. **[14]**

The reported local recurrence rates ranging from 18% to 61% **[1]** The selection of surgical margins (intralesional or extensive excisions) and tumor size (larger or less than 5 cms) were the only identified risk factors for recurrence. **[14]**, **[25]** And the nature of the lesion has little effect on treatment planning and outcome [21] Intraoperatively, the surgeon usually relies on tissue signs such as pulsatility, color changes, bleeding, and refill to determine the margins of resection, but all of which fail to give an exact border to the margin. Some reports show that 40% of cases recur with incomplete excision and 17% of those recur even with macroscopically complete excision. **[7]**, **[26]** [29] Anyway, incomplete attempts only make future surgery both necessary and more difficult as subtotal resection leads to recurrences which are often larger than the primary lesion. So if the lesion is more diffuse the morbidity created by extensive resection has to be weighed against the morbidity of the original disease. The focus of treatment should be improvement of pain, function and appearance. [30] **[14] [5]**

Electrochemotherapy (EChT) is one of little injury methods for malignant tumors newly emerged in the world around 80's of last century.[31] It has been applied on hemangioma and vascular malformations since 90's of last century and has got an excellent results.[32] The fundamental principle of EChT are: D produced strong chemical reactions in the tumor by introducing direct current into it with electrochemotherapy instrument and special electrodes, pH of anodes area decreased to 1-2 and showed strong acidity; pH of cathodes area increased to 12-13 and showed strong alkality; those chemical reactions destroyed erythrocytes、platelets inside the tissues and released hemoglutinin, produced blood clots to form harden of vessel cavity; D direct current induced permeability of the cell membrane increased, removal and diffusion of ions inside of the electric field and induced oxygen and chlorine gas etc, which could kill diseased vessel cells directly; D direct current changed the external and internal environment、destroyed the cell enzymatic active, which induced degeneration and necrosis of protein; D electroosmosis effect: the experimental pathology showed tissues dehydration、constriction of large vessel and capillary and microthrombus formed extensively in anodes areas; interstitial edema capillaries depressed by large fluid accumulation induced obstruction and tissues blood supply destroyed in cathodes; Ddissimilated tissues such as protein sphacelus etc. formed after EChT could be absorbed after 6 months or longer; D the effective style of the electrodes presented a cylinder killing, it's effective diameter is about 10mm.[33], [34]

In our group, 268 cases (53.1%) were performed operative resection and either failure or recurrence, parts of them were operated several times as high as 4 times and remained scar and limbs disturbance. The results produced heavy burden both in economy and psychology on the patients and their relatives.

MRI is the most useful means for the diagnosis of venous malformations, which could confirm the location and extent of the tumor. It's guiding function for treatment is superior than ultrasound wave and CT do. It is less important clinic significance for needling biopsy except when high grade suspect of malignant tumor exist.

EChT avoids hemorrhoea and a rather high incidence rate of limbs disturbance when treated by surgical resection. Most of patients suffered from venous malformations could be treated by EChT.

The only limitation for applying EChT is that tumors close near the important vascular nerve trunk and/or joint cavity.

The common seen complications of EChT are: (1) skin burn in local area; which is usually caused by putting improper position of trocar and applying electric quantity over. The injury could natural repair in most cases; (2) injury of adjacent motor nerve; which is usually caused by putting electrodes near the motor nerve, incomplete injury could natural recover slowly and complete injury could cause permanent disable of limb function.

The poor clinic effect of EChT is caused usually by: (1) the electrodes distributing is unreasonable and don't cover the tumor completely; (2) the electric quantity is not enough; (3) the tumor size is too big or is close motor nerve trunk.

The therapeutic effect is related closely with diseased region and extent. Those need second therapy were mostly tumors of hand and foot or extensive disease and disease close to huge vessels and motor nerve trunk, which usually be managed interval procedures for avoiding complications. It should be cautious when EChT would perform on tumors of hand or foot and which close to important nerve trunk.

Bleomycin and adrenocortical hormone may kill vascular endothelial cell and injure vascular wall, induce vascular smooth muscle cell and endothelial cell apoptosis, make vascular wall thicken and vessel lumens stenosis and atresia at last. It should be one of supplementary treatment for those close to important nerve trunk or residual disease after EChT. [35]

The main indications for MVs of ours include symptomatic relief from persistent or progressive pain, swelling, discomfort, acceleration of tumor growth, functional impairment and cosmetic deformity.

Late recurrences were found to occur relative frequently with this disease, Tang et al. found that most recurrences manifested by 2 years, but some were as late as 6 years after the primary surgery (30% in 5 years postoperatively) **[1]**. And the detection of recurrence relied on the patients' symptoms and/or MRI interpretation, asymptomatic recurrences may have been missed, therefore long-term follow up is necessary to assess adequacy of treatment. **[25], [14]**

Conclusion

EChT has a confirmed therapeutic effect in treating venous malformations, it can improve the patients' symtoms significantly and control the development of the disease. It has the advantages of less trauma, quick recovery, few complication, handled simply, can be performed several times and be easily accepted by patients. It offers a completely new effective method in treating venous malformations.

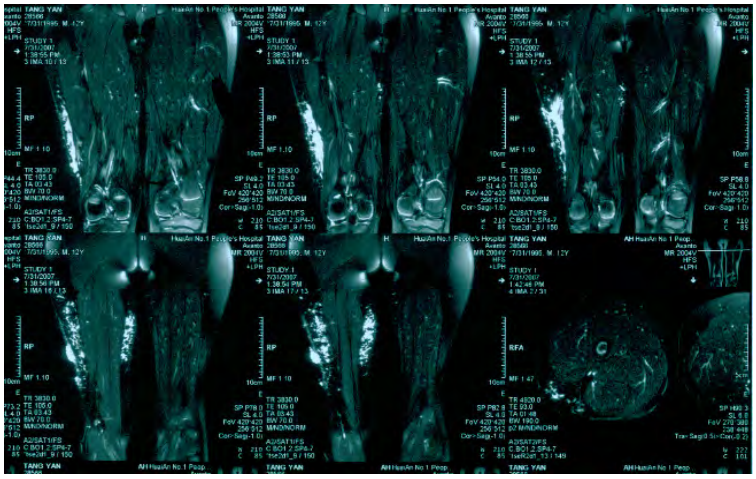
Abbreviations:

VMs: venous malformations
EChT: electrochemotherapy;
MRI: magnetic resonance imaging

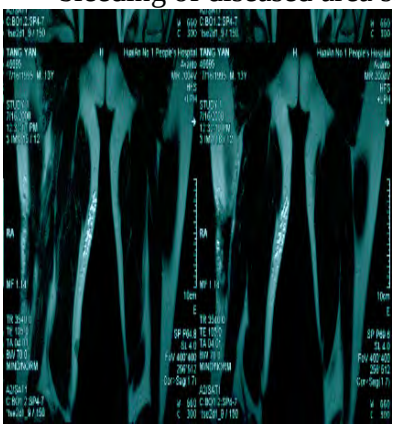
Typical cases

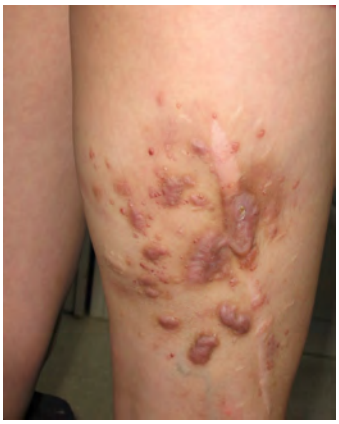
1. Yan Tang, Male, 11 years old. VMs in right thigh and skin involed. Recurrence occurred about 1 year after surgical resection. The diseased area had bleeding intermittently and the patient

complained severe soreness with long time standing and increased physical activity. The picture showed the MRI before EChT.

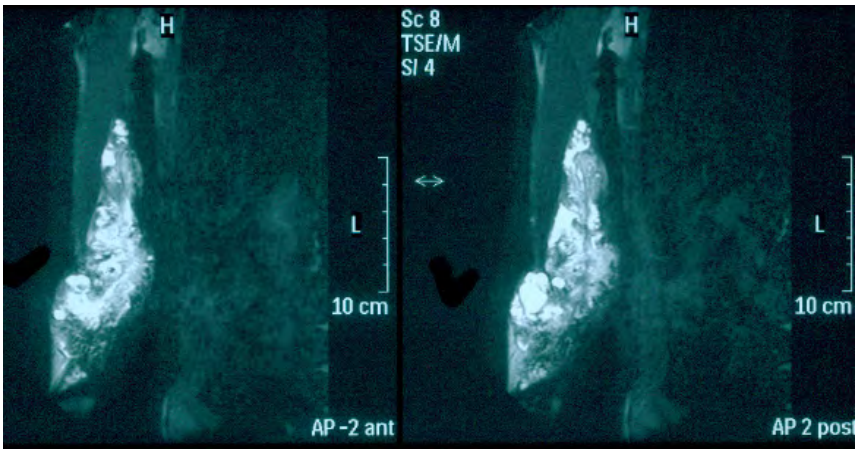


MRI showed most disease disappeared after half year of EChT, the symptom disappeared and bleeding of diseased area stopped with skin sclerosis.

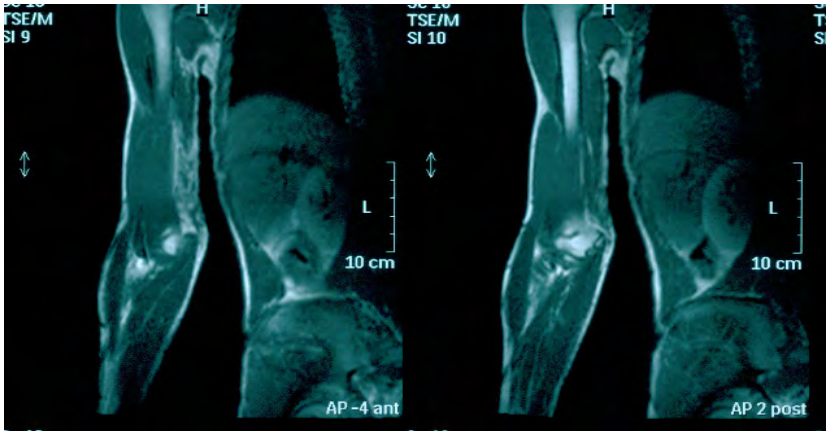




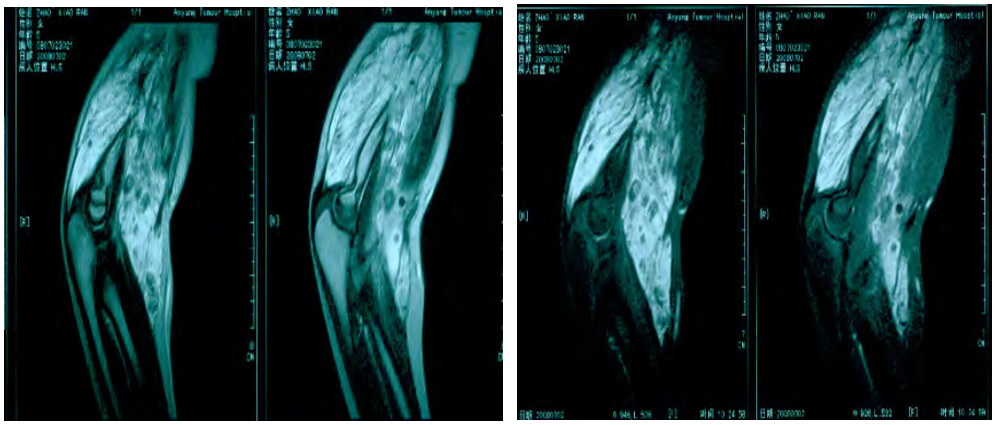
2. Lei Wang, a 13 years old boy. MVs of right upper extremity. Severe soreness with physical activity and function of diseased elbow joint was hindered.



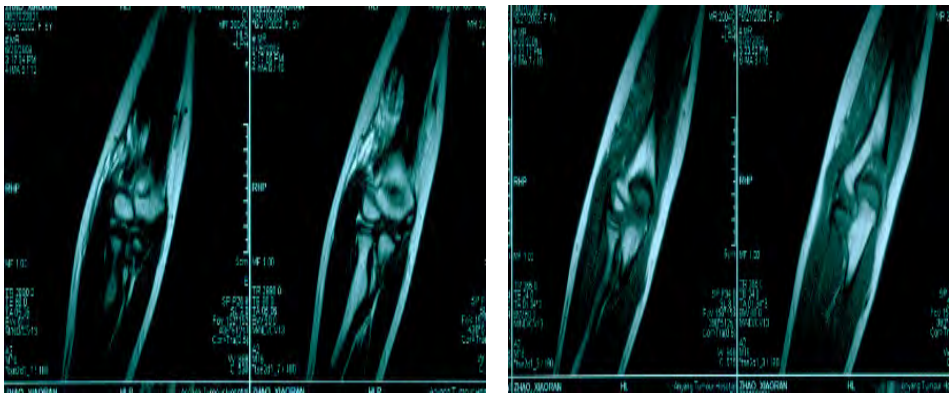
MRI showed most disease disappeared after one year of EChT, the symptom improved and function of diseased elbow appeared normal.



3. Xiao rang Zhao,a 7 years old girl. MVs of right upper extremity. Recurrence occurred about half year after surgical resection and function of diseased elbow joint was hindered.



MRI showed most disease disappeared after one year of EChT, the symptom disappeared completely and function of diseased elbow appeared normal.



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