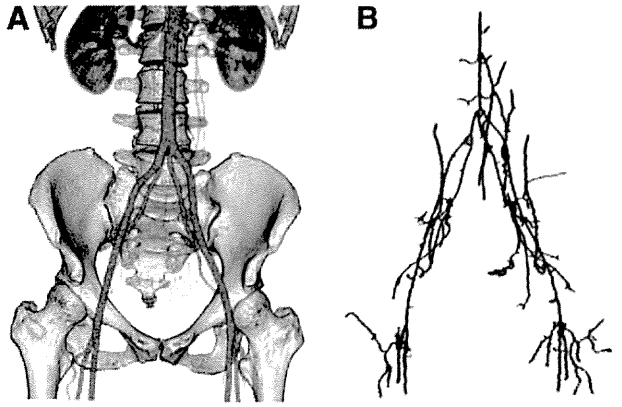

Fig. 2. Representative normal vascular image of control cases (43 years old, female, right breast cancer). A, Enhanced vessels from the level of renal artery to lateral circumflex femoral artery were cropped. B, Skeletonized vascular model shows tree-like structure consisting of internal iliac artery, inferior epigastric artery, lateral circumflex femoral artery, and their branches.

Measurement

The [Analyze Skeleton] command[7] was used on the created model. If the wire frame–shaped vascular structure is considered as a graph (Fig. 1D), the measured values can be used to express it as follows: [Number of nodes] = [Number of junctions] + [Number of end-point voxels] [Number of edges] = [Number of branches]

By substituting these into the equation outlined in a previous study about the mathematical concept of the topological analysis[1]:

$$[\text{Number of vascular loops}] = 1 - [\text{Number of nodes}] + [\text{Number of edges}]$$

we calculated the following: [Number of vascular loops] = 1 − [Number of junctions] − [Number of end-point voxels] + [Number of branches]. The number of vascular loops per vascular lumen unit volume was defined as "loop density", and we then calculated the following:

$$[\text{Loop density}] = \frac{[\text{Number of vascular loops}]}{[\text{Vascular lumen capacity (ml)}]}$$

Statistical Analysis

To evaluate the difference between normal and AVM vessel structure, the Mann–Whitney *U* test was applied to loop density of control group and initial examination of AVM group. To evaluate the topological transformation caused by medical intervention, the Wilcoxon signed-rank test was applied to result of vascular lumen capacity, number of loops, and loop density in both pre- and postprocedural examination.

All statistical analyses were performed using statistical software (IBM SPSS Statistics version 19, IBM, Armonk, N.Y.), and a *P* value <0.05 was considered to indicate a statistically significant difference.

RESULTS

Clinical Findings at Initial Examination

Each AVM patient had 1 lesion site, and all cases were Schobinger stage II or III (Table 2).

Different clinical symptoms were observed at each lesion site. Of the 4 craniocervical cases (cases 1–4), hemorrhage occurred in 3 cases in which progression was noted. However, no cases were accompanied by pain or ulceration of the skin.

The 4 trunk cases (cases 5–8) experienced even fewer symptoms than the craniocervical cases, and 3 cases were classified as Schobinger stage II. Case 5 was the only exception, developing a congested skin ulcer and pulsatile bleeding in the region of the shoulder joint. However, this developed over the shoulder amputation stump that remained after the patient underwent shoulder disarticulation as a child for AVM in the arm. Therefore, this case was similar to a case of AVM of the limbs.

Of the 11 limb cases, the 2 cases proximal to the wrist or ankle (cases 9 and 10) exhibited few symptoms, similar to the trunk cases. However, 6 of the 9 cases distal to the wrist or ankle (cases 11–19) were accompanied by pain due to abnormal circulation. Different phenomenon was observed in the 2 cases (cases 15 and 19) complicated by tissue injury, such as ischemic necrosis of the finger and a stasis ulcer of the foot.

Topological Findings at Initial Examination

Vascular capacity at the initial examination varied from undersized to extremely oversized, ranging from 4.2 ml per lesion (case 13) to 387.0 ml per lesion (case 1). Mean capacity was 57.5 ml.

The number of loops varied from few to extremely numerous, ranging from 13 loops (case 7) to 2634 loops per lesion (case 1). Results for mean values per site with relatively similar resolutions were calculated as 893 loops in the craniocervical region, 197 loops in the trunk region, and 550 loops in the limbs.

Loop density varied according to characteristics, ranging from 0.6 loops/ml (case 7), which was a relatively low-flow cystic lesion, to extreme complexity (case 13), including 113.2 loops/ml. Their weighted average was 9.5 loops/ml, and when compared with loop density indicated by reference CTA data of normal abdominal blood vessels (weighted average, 1.3 loops/ml), AVM lesions exhibited statistically significant greater value ($P < 0.001$) (Fig. 3).

Table 2. Clinical Symptoms and Procedures and CTA Imaging Conditions of AVM Cases

Case No.	Age	Sex	Location		Persistent Pain	Bleeding	Ulceration/ Necrosis	Schobinger Staging	Vascular Lumen Capacity, ml	No. Loops	Loop Density, loops/ml	FOV, mm
1	20	M	Face and scalp	Initial visit	–	+	–	III	387.0	2634	6.8	280
2	38	M	Upper eyelid	Initial visit	–	–	–	II	16.6	467	28.1	230
				10 mo Post partial ablation	–	–	–	II	12.7	277	21.8	
3	50	M	Nose tip	Initial visit	–	–	–	II	8.2	95	11.5	240
				18 mo Untreated	–	+	–	III	6.6	188	28.3	
4	8	M	Buccal region	Initial visit	–	+	–	III	34.2	374	10.9	180
				16 mo Postembolization	–	–	–	II	23.2	58	2.5	
5	71	M	Shoulder	Initial visit	–	+	+	III	52.7	304	5.8	320
				6 mo Post total ablation	–	–	–	II	24.3	75	3.1	
6	32	M	Thoracic wall	Initial visit	–	–	–	II	9.0	91	10.1	345
7	26	F	Thoracic wall	Initial visit	–	–	–	II	20.1	13	0.6	345
				6 mo Post total resection	–	–	–	II	8.7	2	0.2	
8	32	F	Buttock	Initial visit	–	–	–	II	167.4	381	2.3	345
9	30	M	Brachium	Initial visit	–	–	–	II	70.7	332	4.7	200
				9 mo Untreated	–	–	–	II	112.0	778	6.9	
				6 mo Post partial resection	–	–	–	II	24.6	299	12.1	
10	15	F	Forearm	Initial visit	–	–	–	II	6.8	40	5.9	140
				6 mo Post total resection	–	–	–	II	3.6	1	0.3	
11	56	F	Hand	Initial visit	+	–	–	III	15.3	298	19.5	150
12	32	F	Hand	Initial visit	–	–	–	II	15.7	867	55.4	150
13	35	F	Hand	Initial visit	+	–	–	III	16.1	1819	113.2	140
14	61	F	Hand	Initial visit	+	–	–	III	4.2	27	6.4	170
15	43	M	Hand	Initial visit	+	+	+	III	57.1	321	5.6	140
16	45	M	Hand	Initial visit	–	–	–	II	35.2	101	2.9	170
				24 mo Untreated	+	–	–	III	56.4	216	3.8	
17	20	M	Hand	Initial visit	–	–	–	II	51.6	351	6.8	140
				8 mo Untreated	–	+	–	III	54.5	525	9.6	
				12 mo Post total ablations	–	–	–	II	44.1	47	1.1	
18	20	M	Foot	Initial visit	–	–	–	II	80.6	882	10.9	240
19	18	F	Foot	Initial visit	+	+	+	III	44.7	1012	22.7	220

F indicates female; FOV, field of view; M, male.

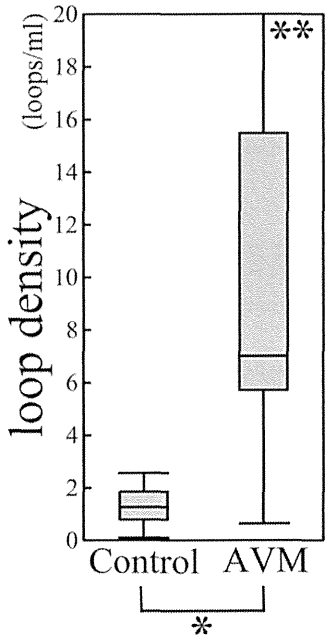

Fig. 3. Loop density comparison of 18 control abdominal vessel data and 19 AVM lesion data. Lines indicate maximum, mean, minimum; and box indicates first to third quartiles.*Statistically significant ($P < 0.001$) in the Mann–Whitney *U* test. **Extra outliers (55 and 113 loops/ml).

When estimated for each site, the weighted average of loop density indicated particularly low in the trunk region, with 3.2 loops/ml compared with 8.0 loops/ml in the craniocervical region and 15.2 loops/ml in the limbs.

Topological Changes According to Progression

Symptomatic exacerbation in the absence of treatment was evaluated in 4 cases (cases 3, 9, 16, and 17).

Measured values revealed that 8–24 months of no treatment caused lesion vascular capacity to obviously increase by approximately 1.5 times in half of the cases (case 9 and 16), whereas lesion vascular capacity showed almost no change or 20% decrease in other cases (cases 3 and 17) (Fig. 4A).

Although the number of cases was not enough for statistical verification, loop number and density both increased in all cases without treatment (Figs. 4B, C). In particular, the loop number increased greatly by 2 times or more in 3 cases (cases 3, 9, and 16). Meanwhile, the rate of changes in loop density became dull compared with that of loop number because of increased vascular lumen capacity in cases 9 and 16.

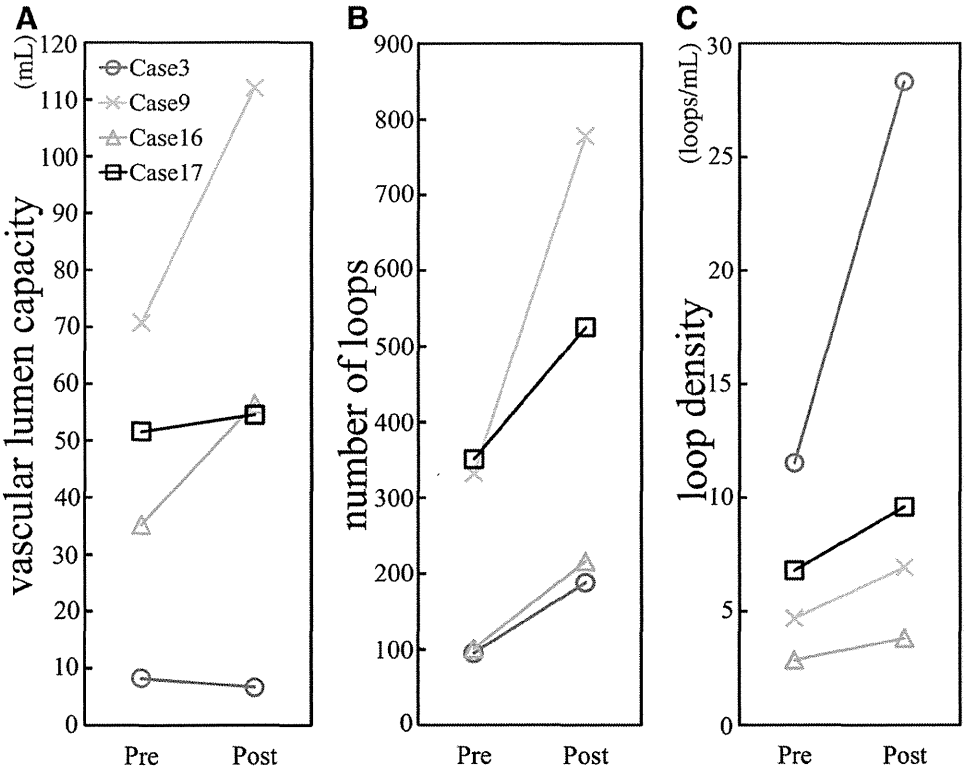

Fig. 4. Topological changes according to progression (cases 3, 9, 16, 17). Statistical verification test was not applied because of insufficient number of cases. A, The lesion vascular capacity decreased in all cases except case 3 (underwent sutures for hemostasis). B, Total loop number clearly increased in all cases without treatment. C, Loop density increased in all cases, but vascular lumen expansion made changes dull in cases 9 and 16.

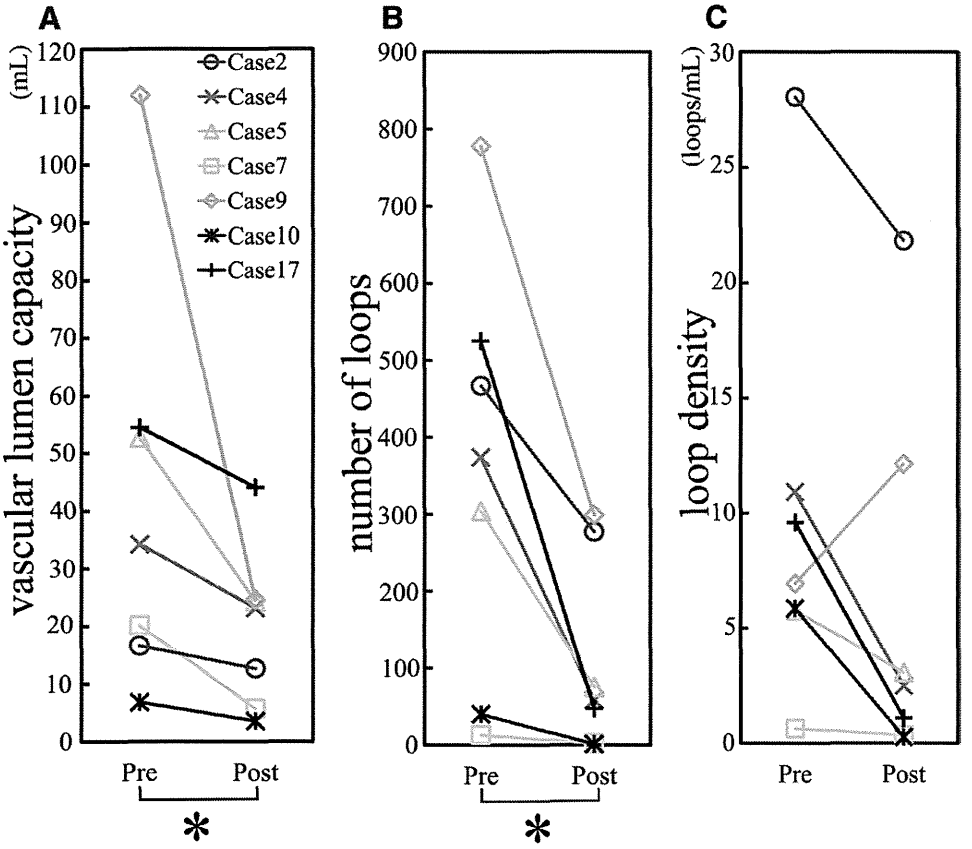

Fig. 5. Topological changes caused by treatment (cases 2, 4, 5, 7, 9, 10, 17). *Statistically significant ($P = 0.0156$). A, Vascular lumen capacity in the lesion area significantly decreased in all cases. B, Number of loops significantly decreased in all cases. The decrease was clear in the total treatment cases (cases 4, 5, 7, 10, 17) and dull in the partial treatment cases (cases 2 and 9). C, Changes in loop density differed according to the scale of treatment. Clear decrease was noted in entire treatment cases (cases 4, 5, 7, 10, 17), and the values barely changed in partial treatment cases (cases 2 and 9).

Topological Changes Caused by Treatment

Therapeutic effects were evaluated in 7 cases (cases 2, 4, 5, 7, 9, 10, and 17).

Surgical resection was performed in cases 7, 9, and 10; however, the resection range was limited within subcutaneous tissue to preserve biceps brachii muscle in case 9 (partial resection). Cicatrization using radiofrequency ablation[8] as a preparation for resection was performed in cases 2, 5, and 17; however, the ablation range was limited within subcutaneous tissue to preserve the levator palpebrae superioris muscle in case 2 (partial ablation). In case 4, endovascular embolization with n-butyl cyanoacrylate was performed.

Regardless of the type of treatment conducted, vascular lumen capacity in the lesion area decreased in all cases to 28%–81% compared with previous values (Fig. 5A), and that change was statistically significant ($P = 0.0156$).

The number of loops also decreased in all cases because of treatment (Fig. 5B), and statistical significance was indicated ($P = 0.0156$). However, the strength of therapeutic effects differed according to the scale of treatment, with 75%–98% loops disappearing in the total resection/ablation/embolization cases (cases 4, 5, 7, 10, and 17), whereas only 41%–64% disappeared in the partial resection/ablation cases (cases 2 and 9).

The scale of treatment also influenced changes in loop density (Fig. 5C). Although a clear decrease was noted in the 5 cases (cases 4, 5, 7, 10, and 17) where treatment targeted the entire lesion and an approximately 95% decrease was observed in case 10, the values barely changed in the 2 cases that underwent partial treatment (cases 2 and 9). Furthermore, records showed that in case 9, loop density exhibited a temporary postoperative increase of approximately 2.5 times compared with preoperative data.

DISCUSSION

Significance of Each Parameter

Our analysis indicated that AVMs have denser vascular loops than normal vessels, and their progres-

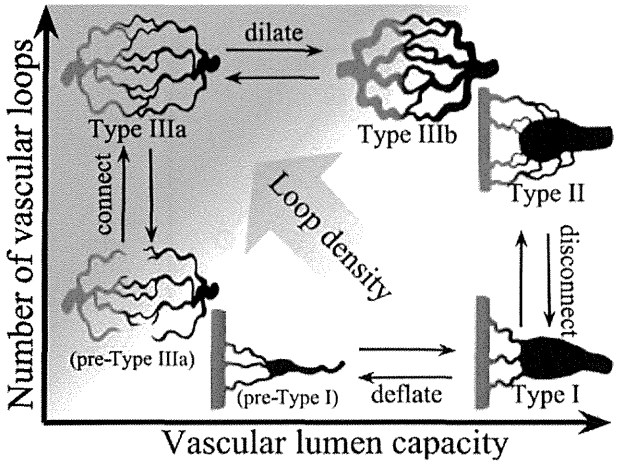

Fig. 6. Mutual transition between various types of AVMs are expected from a geometrical viewpoint. Classification by Cho et al.[10] Types I and II are considered to be a close relation differentiated by their connectivity. Types IIIa and IIIb are considered to be a close relation differentiated by their vascular diameter. Type I with lower vascular lumen capacity (as it were pre–type I) and type IIIa with fewer vascular connections (as it were pre–Type IIIa) are similar to normal vessel structures and sometimes overlooked as subclinical AVMs. Type I sometimes shows lower loop density than normal.

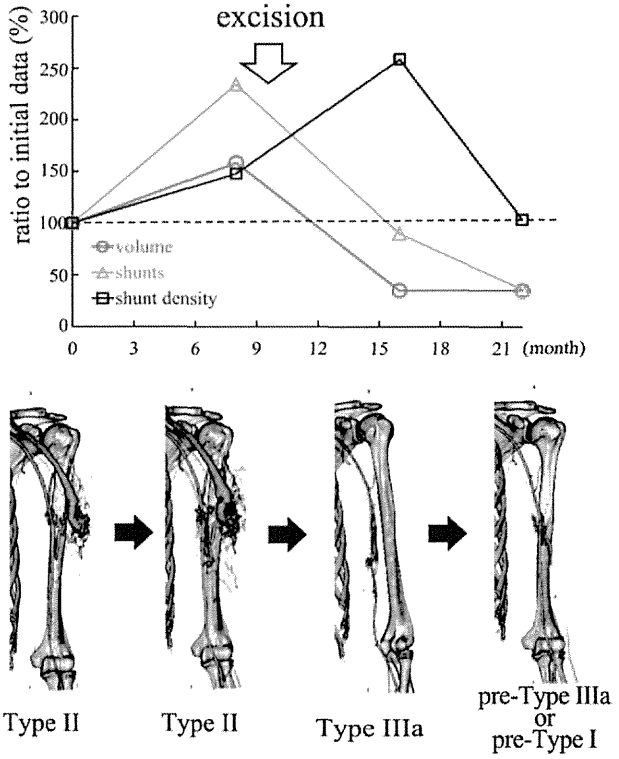

Fig. 7. Detailed course, 3D CTA images, and their AVM morphology (classification by Cho et al[10]) of case 9 (30 years old, male, left brachial AVM). At initial examination and 9 months untreated, the AVM morphology was type II, which contains dilated venous cavity. Six months after surgery, the volume of the lesion had greatly decreased due to resection of nidus which mainly consists of a dilated venous cavity, and remaining plexiform arteriolovenulous shunts (type IIIa) caused a temporary increase in loop density. Twelve months after surgery, excessive microscopic shunts regressed without having much effect on vascular lumen capacity, reducing loop density. But a lesion with smaller scale and unchanged loop density from the initial examination is persistent in the end.

sion is accompanied by an increase in the number and density of vascular loops contained within the lesion. However, increase in loop density itself does not necessarily reflect the progression of the lesion. Loop density is only indicative of lesion shape.

Even in lesions with the same number of loops, high loop density indicates a lesion with diffuse microscopic arteriovenous fistulas and percutaneous/transcatheter interventional radiology is likely to be difficult. In contrast, low loop density represents a tortuous feeding artery or an abundance of cavities in a dilated arterialized vein and is indicative of a high risk for hemorrhage if surgery is conducted.[9,10] Dynamically, increased loop density signifies that "the lesion has increased its internal connections or has deflated." In contrast, decreased loop density signifies that "the lesion has decreased its internal connections or has expanded" (Fig. 6).

Applicability to Prediction of Course

Of all the treatment cases, case 9 provided most data regarding morphological changes in the lesions over the course of treatment (Fig. 7). The AVM morphology in this case was type II according to the classification by Cho et al,[10] and the proportion in the dilated venous cavity side of the extracted lesion increased.

Therefore, although the volume of the lesion had greatly decreased 6 months postoperatively, transition to type IIIa plexiform arteriolovenulous shunts remaining in the area may have caused a temporary increase in loop density. Data at 12 months after surgery showed that excessive microscopic shunts regressed without having much effect on vascular capacity, reducing loop density.

Despite this, because the loop density (lesion shape) itself is approximately the same as at the time of the initial examination, we can be cautioned that the results of this surgery are only about the same as palliation to arteriovenous fistula–like, as it were pre–type IIIa or pre–type I state, and in fact, this brachial AVM relapsed 1 year later from the last CTA inspection.

Mathematical analysis was useful for evaluating the risk of relapse in this instance, as the case continually exhibited few symptoms and remained at Schobinger stage II over the course of its development, whereas on CTA images, it appeared that the lesion had gone into remission macroscopically.

In contrast, although symptoms of case 5 disappeared dramatically with treatment, changes in

vascular structure could not be discerned macroscopically from CTA images (Fig. 8).

However, the decreased vascular capacity, loop number, and loop density indicated by mathematical analysis depict the fact that the blood vessel of the lesion in this patient developed from a thick abnormal mesh into a thin normal tree, and in fact, no relapse of this shoulder AVM has been observed at the present moment of 3 years after surgery.

CONCLUSIONS

In conclusion, although this was a pilot study with a limited number of cases, application of topological analysis showed that the density of vascular loop structures in AVMs was more than that of normal vessels, and a lack of treatment in the same patient led to an increase in the number of loops, whereas treatment led to a decrease in the number. As symptoms and CTA imaging conditions for AVMs vary according to the site, this technique needs to be refined and standardized to obtain more testing data, which could be used for a better prediction of the course of AVMs. Our analysis is a technique that can be practiced immediately and cheaply by any clinician with a combination of already commonly used CT equipment, a low-end personal computer, and multiplatform open source softwares. Because AVMs can exist beyond the soft tissues, including the brain, lungs,

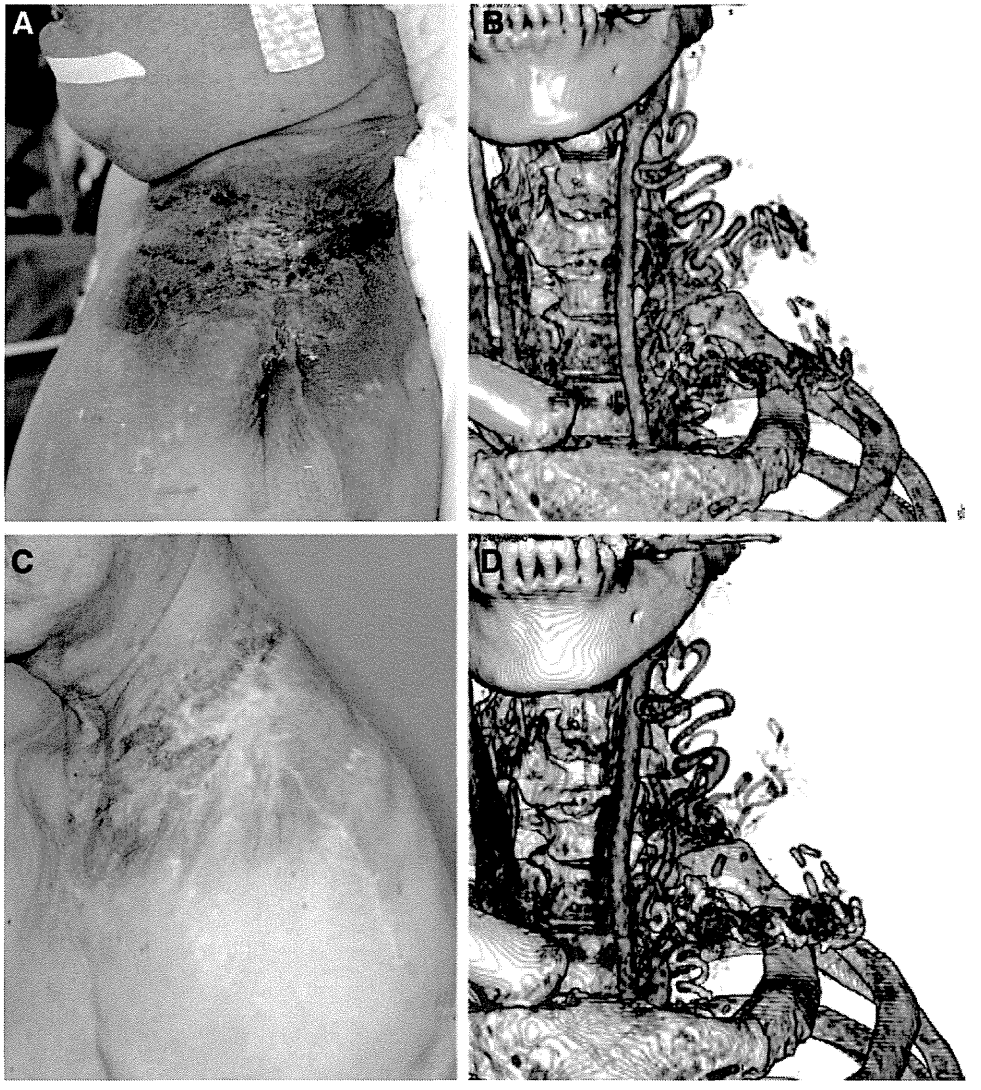

Fig. 8. Case 5 (71 years old, male, left shoulder AVM): a representative case in which changes in vascular structure could not be discerned macroscopically, despite symptoms disappeared dramatically with treatment and topological analysis showed normalization of vascular structure. A and B, Preoperative condition and 3D CTA image. The patient was having chronic ulceration and abrupt pulsatile bleeding during sleep. C and D, Six months postoperation. The chronic ulcer has totally epithelized. Macroscopically, changes in vascular structure could not be discerned from CTA.

and intraperitoneal organs, this technique can be broadly tested by other clinical departments.

Yuki Hata, MD
Department of Plastic Surgery
Osaka University Graduate School of Medicine
Osaka, Japan
E-mail: yukihata@gmail.com

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Percutaneous sclerotherapy for venous malformations in the extremities: clinical outcomes and predictors of patient satisfaction

Masahisa Nakamura[1*], Keigo Osuga[1], Noboru Maeda[1], Hiroki Higashihara[1], Kenichiro Hamada[2], Nobuyuki Hashimoto[3], Shuichiro Uehara[4] and Noriyuki Tomiyama[1]

Abstract

The purpose of this study is to retrospectively evaluate the clinical outcomes and to identify the predictors ofpatient satisfaction after percutaneous sclerotherapy for venous malformations (VMs) in the extremities. A totalof 48 patients with VMs in the extremities over 10 years of age underwent sclerotherapy to relieve symptoms, such as pain, swelling, functional limitations, and cosmetic problems. Self-assessment questionnaires were sentto rate the degree of symptom improvement and level of satisfaction. Clinical and imaging data from medicalrecords were analyzed to obtain information about VMs and sclerotherapy. The predictors for patientsatisfaction were determined by univariate and multivariate analysis of clinical variables. Forty patients (meanage, 28.2 years; range, 11-69 years) responded to the survey. Sixteen patients had VMs in the upper extremities, and 24 patients had VMs in the lower extremities. In 12 patients (30%), adjacent bone change was seen. After amean of 2.6 (range 1-10) sclerotherapy sessions, good response to pain, swelling, dysfunction, and cosmeticproblems was obtained in 83%, 74%, 79%, and 50% of patients, respectively. Thirty-two patients (80%) weresatisfied with their outcomes. On univariate analysis, absence of adjacent bone change, maximum diameter (<6.7 cm), and number of sclerotherapy sessions (<3) were significantly associated with patient satisfaction.Multivariate analysis revealed absence of adjacent bone change (odds ratio, 7.56; 95% confidence interval, 1.02-55.8) as an independent predictor for satisfaction. Thus, adjacent bone change significantly portended adissatisfied patient. In conclusion, percutaneous sclerotherapy was effective to relieve symptoms of VMs in theextremities, and most patients were satisfied with the outcomes. However, adjacent bone change was asignificant predictor of patient dissatisfaction.

Keywords: Venous malformation; Sclerotherapy; Extremity; Adjacent bone change; Predictor

Introduction

Venous malformations (VMs) are the most common type of vascular malformations. VMs are comprised of dilated, thin walled, sponge-like abnormal channels with deficient smooth muscle (Mulliken & Glowacki 1982). They are located in any portion of the body, and the main locations are the extremities (40%), the head and neck (40%), and the trunk (20%) (Dubois & Garel 1999). VMs in the extremities are sometimes asymptomatic but often present with various symptoms of pain, swelling, functional limitations, cosmetic disfigurements, and so on (Mendonca et al. 2010). Surgery, sclerotherapy, laser therapy, and conservative treatments such as elastic compression garments have been used for the management of VMs (Van der Vleuten et al. 2014). Sclerotherapy has also played a central role as a minimally invasive and effective treatment (Van der Vleuten et al. 2014; Berenguer et al. 1999; Tan et al. 2007).

Not all the outcomes of sclerotherapy for VMs have been satisfying, however, and overly aggressive treatment can make the condition worse rather than improve it and result in serious complications (Lee et al. 2008). A few studies (Berenguer et al. 1999; Yun et al. 2009) have evaluated predictors of response after sclerotherapy by

* Correspondence: m-nakamura@radiol.med.osaka-u.ac.jp
[1]Department of Diagnostic and Interventional Radiology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka Suita, Osaka 565-0871, Japan
Full list of author information is available at the end of the article

multivariate analysis. Identification of response predictors is clinically useful to help guide patient selection and might thereby help improve treatment results and minimize complications. The clinical manifestations of VMs vary according to anatomic locations. However, predictors for response to sclerotherapy for extremities VMs have not yet been identified. The aim of this study was to evaluate clinical outcomes and predictors for patient satisfaction after sclerotherapy for VMs in the extremities.

Materials and methods

Patients

Following approval from the Institutional Review Board, we performed a retrospective study of a clinical database for 128 patients treated with sclerotherapy in our department between December 2002 and May 2012. The inclusion criteria for the present study population were: patients over 10 years of age who had undergone sclerotherapy for VMs in the extremities; the sclerotherapy treatment was considered to be finished; and more than 6 months had passed since the last treatment. Patients with combined vascular malformations (e.g., capillary VMs, lymphatic VMs, capillary-lymphatic VMs, Klippel-Trenauney syndrome) were excluded. Six patients who underwent surgical resection after sclerotherapy were also excluded.

VMs were diagnosed by a combination of clinical examination and noninvasive studies, such as magnetic resonance imaging (MRI), duplex ultrasonography (US), and plain film radiography, and were confirmed by fluoroscopic imaging using direct puncture. The treatment modality was determined by a multidisciplinary team in our vascular malformation clinic, involving interventional radiologists, plastic surgeons, orthopedists, pediatric surgeons, dermatologists, and pathologists. The indications for invasive treatment included worsening pain, increased swelling, reduced function, and severe cosmetic disfigurement, based on balance between the degree of symptoms and the risk of intervention.

Among 128 patients treated with sclerotherapy, 48 patients who met the inclusion criteria were contacted by telephone and were sent a questionnaire. Forty patients who submitted self-assessment data were included in the study.

Procedures

After proper counseling and after obtaining written informed consent from patients/parents, treatment of VMs was performed using direct percutaneous injection of 3% polidocanol, absolute ethanol, or 5% ethanolamine oleate (EO). Treatment for VMs was typically tailored to each lesion and to each patient; therefore, it was not possible to utilize a uniform treatment protocol. As sclerosants, 3% polidocanol foam was mainly used. When polidocanol was not effective, we tended to use ethanol or EO. General anesthesia was used when performing ethanol injection. Otherwise, conscious sedation and local anesthesia were chosen for pain control.

Direct puncture of the lesion was performed using a 21- to 27-gauge needle under ultrasound guidance or by direct observation. Multiple punctures were performed to inject sclerosant into the majority of the lesion. The volume injected was based on the patient's weight and on the size of VM. The maximum dose of polidocanol, ethanol, and EO injected per person was 10 ml, 0.4 ml/kg, and 0.4 ml/kg, respectively.

The decision to perform repeat sclerotherapy was based on a discussion with the patient. The goal of treatment was not to eliminate the lesion, but rather to improve symptoms. Thus, even if the lesion persistent, treatment was discontinued if those goals were achieved (Figures 1).

Complications were classified into major or minor complications, according to Society of Interventional Radiology reporting standards (Omary et al. 2003). Major complications were those that resulted in an unplanned increase in the level of care, permanent adverse sequelae, or death. Minor complications were those that resulted in no sequelae with or without nominal therapy requirement.

Questionnaire

A self-assessment questionnaire was sent to the patients in December 2012. The questionnaire contained items assessing symptoms and satisfaction levels. In the questionnaire, patients were asked for specific symptoms (e.g., pain, swelling, functional limitations, and cosmetic disfigurements), and a four-point scale was used to rate the degree of symptom improvement as follows: markedly improved, moderately improved, no change, and worsening (van der Linden et al. 2009). Similarly, patients were asked whether they were satisfied with sclerotherapy as follows: very satisfied, satisfied, dissatisfied, or neither. "Markedly improved" and "improved" were defined as a "good response", and "very satisfied" and "satisfied" were defined as "satisfaction".

Clinical variables

Data with regard to patient demographics, clinical assessments, imaging studies, treatments, and treatment complications were obtained from the medical charts and imaging, as collected by two of the authors (MN and KO). All patients underwent pre-MRI. Clinical variables included demographic (sex), and imaging variables (VM location, VM size, VM margin, adjacent bone change, and anatomical pattern of draining veins on direct puncture venography), and procedure variables (the number of sclerotherapy, and sclerosants). Parameters that were proposed as predictors of outcomes in previous studies were evaluated in the present study (Berenguer et al. 1999; Puig et al. 2003; Yun et al. 2009; Jin et al. 2009; Mimura et al. 2009; Mendonca et al. 2010). Although adjacent bone changes, such as periosteal reaction,

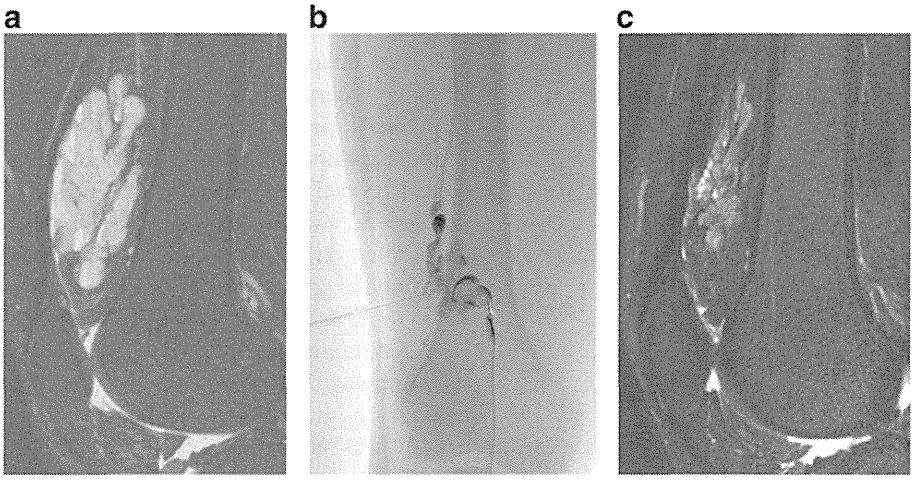

Figure 1 A 30-year-old-male with pain, swelling, and dysfunction of the right knee joint. A. The sagittal fat-saturated T2-weighted MR image before treatment shows a lobulated high-intensity mass in the suprapatellar bursa. **B**. Direct puncture phlebography shows the lesion cavity and the conducting vein (Type 2). Sclerotherapy was performed with 3% polidocanol foam. **C**. After two sessions, MR imaging shows a decrease in size and signal intensity of the mass. The patient had improvement of symptoms and indicated satisfaction on the questionnaire.

cortical irregularity including thickening or erosion, and medullary signal change, are often seen in VMs involving deep tissues (Ly et al. 2003), this change has not been evaluated a predictors of outcomes in previous reports. Thus, we studied whether "adjacent bone change" on MRI and plain film radiography was a predictor of outcomes in our study. The diameters of lesions were measured using MR images. Based on MRI, VMs were categorized into two margin types: a well-defined margin was defined as a sharp transition from surrounding tissue (n = 17), whereas an ill-defined margin was defined as an irregular interface with surrounding tissue (n = 23) (Jin et al. 2009). With regard to anatomical pattern of draining veins on direct puncture venography, we classified VMs into to the four types; Type 1 – isolated malformation without peripheral drainage, Type 2 – malformation that drains into normal veins, Type 3 – malformation that drains into dysplastic veins, Type 4 – malformation that represents a dysplasia (Puig et al. 2003). In our study, no lesions of Type 4 were included.

Statistical analysis

We evaluated predictors of patient satisfaction, performing uni- and multivariate analysis of the clinical variables. The cut-off score for patient age, VM size, and the number of sclerotherapy treatments were determined by receiver operating characteristic (ROC) curve analysis. Univariate analysis was performed to compare variables between the "satisfaction" group and the "non-satisfaction" group using the chi-square test and the Kruskal-wallis test. For multivariate analysis, a binary logistic regression model was used to identify independent predictors. P values of less than 0.05 were considered to indicate statistical significance. Statistical analysis was performed using SPSS Statistics 21 software (IBM Corporation, USA).

Results

Patient demographics and clinical data were summarized in Table 1. Distribution of the lesions in the extremities was given in Table 2. A total of 105 treatment sessions

Table 1 Patient demographics and clinical data

Variables	n = 40
Age[a]	28.2(11–69)
Sex (male:female)	11:29
Location of VM[b]	
Upper extremity	16(40)
Lower extremity	24(60)
Previous treatment[b]	
Operation	11(28)
with sclerotherapy	2(5)
with TAE	1(3)
Number of sclerotherapy treatments[a]	2.6(1–10)
Sclerosants (partially overlapped)[b]	
Polidocanol	37(93)
Absolute ethanol	11(28)
Ethanolamine oleate	6(15)
Dose of sclerosants (ml)/session[a]	
Polidocanol	2.8(0.4-7.0)
Absolute ethanol	7.4(4.0-13)
Ethanolamine oleate	11.1(4.5-20)

[a]Data are means. Numbers in parentheses are the range.
[b]Data represent number (percentages) of patients.

Table 2 Distribution of the lesions in the extremities

Sites		N	Total
Upper extremity			16
	Shoulder	2	
	Upper arm	4	
	Elbow	3	
	Forearm	1	
	Hand	4	
	Multiple	2	
Lower extremity			24
	Buttock	2	
	Upper leg	6	
	Knee	2	
	Lower leg	6	
	Foot	7	
	Multiple	1	
Total			40

were performed (mean, 2.6 sessions per patient; range, 1–10 sessions). The mean number of punctures per session was 5.9 (range, 1–27). The sclerosants used for treatment are listed in Table 1. Polidocanol was used in a majority (37 of 40) of patients. In five patients, pneumatic cuff tourniquets were used beyond the lesion's venous outflow. The mean follow-up period was 2.3 years (range, 7 months-7.5 years).

Two major complications occurred after sclerotherapy. One patient treated with 10.5 ml of absolute ethanol had peroneal nerve paralysis for 9 months (Figures 2). The other patient treated with 20 ml EO had acute renal failure and needed temporary hemodialysis. Minor complications like local swelling and pain were experienced in most cases for a few days and were well controlled with NSAIDs.

Patient self-assessment questionnaire results are given in Table 3. Before treatment, 36 of the 40 patients (90%) had disabling pain, 34 (85%) had swelling, 24 (60%) had functional limitation, and 16 (40%) had cosmetic disfigurement. Patients reported "good response" in pain (83%; 30/36), swelling (74%; 25/34), functional limitation (80%; 19/24), and cosmetic disfigurement (50%; 8/16). "Markedly improved" was noted in at least one category in 48% (19 of 40) of patients. None of the patients responded "worse" for any symptoms. In addition, 32 of 40 patients (80%) reported being "very satisfied" or "satisfied" with the treatment; these patients were defined as the "satisfaction" group.

On univariate analysis of variables to predict satisfaction with sclerotherapy, absence of adjacent bone change, maximum diameter (<6.7 cm), and number of sclerotherapy sessions (<3) were significantly associated with patient satisfaction (Table 4).

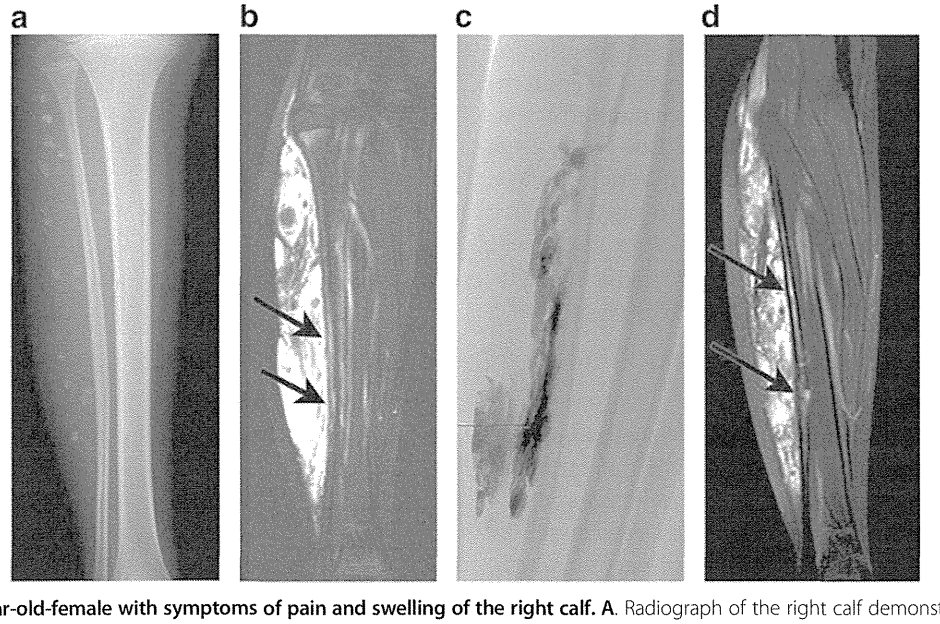

Figure 2 A 12-year-old-female with symptoms of pain and swelling of the right calf. A. Radiograph of the right calf demonstrates phleboliths and cortical irregularity in the fibula. **B**. The coronal fat-saturated T2-weighted MR image before treatment shows a large and infiltrating mass adjacent to the fibula with diffuse marrow signal abnormality (arrows). **C**. Direct puncture phlebography reveals VM with dysmorphic veins and early venous return of the peroneal vein (Type 3). After sclerotherapy with ethanol, the patient had onset of temporary peroneal nerve paralysis. **D**. Although the lesion shows a decrease in thickness and signal intensity on MRI, the marrow signal abnormality (arrows) remains unchanged. She reported no change in symptoms and indicated dissatisfaction on the questionnaire.

Table 3 Clinical outcomes and degree of satisfaction after sclerotherapy

Symptom	Marked improvement	Improvement	No change	Worse	Total
Pain	13(36)	17(47)	6(17)	0	36
Swelling	11(32)	14(41)	9(26)	0	34
Functional limitations	10(42)	9(38)	5(20)	0	24
Cosmetic disfigurements	3(19)	5(31)	8(50)	0	16
	Very satisfied	Satisfied	Neither	Dissatisfied	Total
Satisfaction	16(40)	16(40)	4(10)	4(10)	40

Note. Numbers in parentheses are percentages.

Table 5 shows the result of multivariate analysis. Absence of adjacent bone change (odds ratio, 7.56; 95% confidence interval, 1.02-55.8) was the only independent predictor of patient satisfaction. Among 27 (68%) patients with VMs adjacent to the bones, 12 patients (30%) showed the adjacent bone change (Figures 3).

Table 4 Univariate analysis of variables to predict satisfaction with sclerotherapy

Variables	Satisfaction	Non-satisfaction	P value
Patient demographics			
Sex			0.051
Male	11	0	
Female	21	8	
Location of VM			0.333
Upper extremity	14	2	
Lower extremity	18	6	
Imaging variables			
Maximum diameter of VM			0.018
<6.7 cm	19	1	
≥6.7 cm	13	7	
Margin on MRI			0.055
Limited	16	1	
Infiltrating	16	7	
Adjacent bone change			0.002
Absent	26	2	
Present	6	6	
Anatomical pattern of draining veins			0.361
Type 1	19	3	
Type 2	8	2	
Type 3	5	3	
Procedure variables			
Session number of sclerotherapy[a]			0.014
<3	23	2	
≥3	9	6	
Sclerosants			0.32
Polidocanol only	22	4	
Other	10	4	

[a]The Kruskal-wallis test.

Discussion

A comprehensive classification of vascular anomalies was accepted by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996 (Enjolras & Mulliken 1997). Two major categories of lesions emerged: vascular tumors and vascular malformations. Differentiating between vascular tumors and malformations is essential, as their clinical, radiological and pathologic features differ. Further, their associated morbidity and their management are quite different. VMs are low-flow vascular malformations and can infiltrate skin, muscles, joints, and sometimes bones. In 2013, a "modified" Hamburg classification was adopted to emphasize the importance of extratruncular vs. truncular sub-types of VMs; ISSVA Classification was reinforced with an additional review on syndrome-based classification (Lee et al. 2014). The new classification incorporated the embryological origin, morphological differences, unique characteristics, prognosis and recurrence rates of VMs based on this embryological classification.

Symptoms are dependent on the anatomic location of the lesion. Pain and swelling are common symptoms associated with all VMs. With craniofacial lesions, cosmetic disfigurement may be more debilitating than functional limitations (Lee & Chen 2005). In contrast, the management of VMs in the extremities is often difficult due to functional problems rather than cosmetic concerns (Mendonca et al. 2010). In this series, 24 patients (60%) reported functional limitations. Thus, we focused on VMs in the extremities.

Sclerotherapy is now the primary treatment of choice for VMs. Several sclerosants have been proven effective and vary in their mode of action and relative toxicity (Van der Vleuten et al. 2014). Currently, there is no consensus as to the best sclerosant. All sclerosants are associated with potential complications, including skin necrosis, peripheral nerve injury, hemoglobinuria, thromboembolism, infection and delayed muscle fibrosis (Burrows 2013). We mainly use polidocanol, because it has sufficient effect and because it is associated with lower major complication rates (Blaise et al. 2011). Indeed, in our

Table 5 Multivariate analysis of variables to predict satisfaction with sclerotherapy

Variables	P value	Odds ratio	95% confidence interval
Absence of adjacent bone changes	0.048	7.56	1.02-55.8
Maximum diameter (<6.7 cm)	0.308	3.70	.299-45.8
Session number of sclerotherapy (<3)	0.240	3.56	.429-25.5

cohort, there were no major complications after sclerotherapy using polidocanol.

The efficacy of sclerotherapy for VMs is difficult to evaluate, as there are no standard assessment criteria (Rautio et al. 2004). We attempted to evaluate treatment outcomes according to overall patient satisfaction and subjective patient response using a self-assessment questionnaire rather than attempt to quantify morphologic response (van der Linden et al. 2009). This is because lesion sizes and symptoms of VMs vary widely and there is often discrepancy between the clinical and morphologic responses to sclerotherapy (Tan et al. 2007; Yun et al. 2009).

Our analysis of a cohort of 40 patients who responded to follow-up questionnaires showed that 80% of patients were satisfied with treatment outcome and that only two major complications (5%) occurred. Pain, swelling, and functional limitations were improved in about 80% of patients, whereas cosmetic improvement was seen in 50% of patients. Van der Vleuten et al. (2014) conducted a systematic review of studies investigating treatment for VMs. They reported that sclerotherapy was effective in 65% to 90% of cases. Our results are comparable to those seen in previous reports and indicate that sclerotherapy was minimally invasive and effective as a primary treatment for VMs.

Identification of predictors of response to sclerotherapy is important to optimize outcomes through appropriate

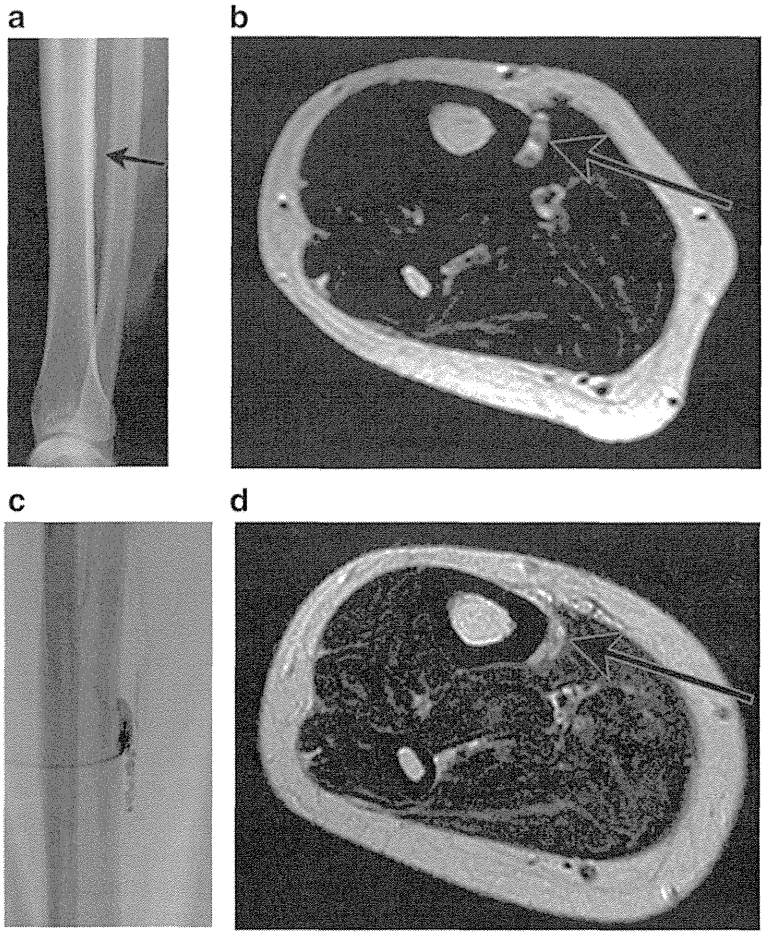

Figure 3 A 37-year-old-female with symptoms of severe pain of the right lower leg. A. Radiograph of the right lower leg demonstrates tiny periosteal reaction in the tibia (arrows). **B**. The axial T2-weighted MR image before treatment shows a tiny lesion adjacent to the tibia with cortical irregularity (arrows). **C**. Direct puncture phlebography reveals VM with normal veins and early venous return (Type 2). Sclerotherapy was performed with 3% polidocanol foam. **D**. Although the lesion decreased in size and signal intensity on MRI (arrows), she answered no change in symptoms and dissatisfaction on the questionnaire.

patient selection. Previous reports have investigated predictors of response to sclerotherapy in VM patients. For example, Berenguer et al. (1999) reported that male sex and number of sclerotherapy sessions were independent predictors of good outcomes. Goyal et al. (2002) proposed that patients with well defined, small VMs on MRI imaging had a better response to sclerotherapy. Yun et al. (2009) identified no or delayed visualization of drainage veins, a well-defined margin on MRI, and female sex as predictors of good outcomes. Mimura et al. (2009) revealed a better therapeutic effect in patients with small VMs, well-defined VMs, and VMs with good stasis of sclerosant during sclerotherapy.

In our study, adjacent bone change, maximum diameter of VM, and number of sclerotherapy sessions were significantly associated with patient satisfaction on univariate analysis. Multivariate analysis revealed that absence of adjacent bone change was an independent predictor for good satisfaction after sclerotherapy, whereas sex, VM location, VM margin, and anatomical pattern of draining veins on a venography were not. Thus, poor outcomes are expected in VMs with adjacent bone change. Mendonca et al. (2010) estimated that VMs with bone or joint involvement were associated with a higher risk of symptom recurrence. Goto et al. (2001) reported that hemangiomas with adjacent periosteal new bone formation were more painful than those without it. These results support our findings.

Bone changes adjacent to VMs (also referred to as "soft-tissue hemangiomas" in the literature) were observed in 19-63% of patients on plain film or MRI (Mendonca et al. 2010; Ly et al. 2003; Goto et al. 2001; Sung et al. 1998; Enjolras et al. 1997; Breugem et al. 2001; Pourbagher et al. 2011). In our cohort, 12 patients (30%) had bone changes adjacent to VMs. The precise mechanism of adjacent bone change remains unknown. Several factors could contribute to adjacent bone change, including physical irritation, an extrinsic pressure and passive hyperemia (Sung et al. 1998; Goto et al. 2001; Pourbagher et al. 2011). Bone homeostasis is maintained by the balance between bone resorption and formation and is affected by local oxygen tension and pH, various cytokines, and hormones (Arnett 2010). We postulate that some cytokines and the change in local oxygen tension and pH due to latent microshunts and congestion may be one of the important factors developing the adjacent bone change around VMs, but it is still no better than a conjecture.

Further investigation is needed to clarify the effect of adjacent bone change on patient symptoms that may impair patient satisfaction to sclerotherapy. Studies of local oxygen tension and pH, bone metabolic markers of osteoblast and osteoclast function, and some cytokines might be useful in this regard.

This study had several limitations. First, the study was retrospective and had a small number of patients. Further, there were no standards for treatment indication and evaluation criteria for sclerotherapy of VMs. In addition, we did not evaluate patient mental health that may affect patient satisfaction. We may take account of the use of validated quality-of-life assessment tool, such as SF-36 and the Child Health Questionnaire (CHQ).

In conclusion, percutaneous sclerotherapy was effective in relieving symptoms in patients with VMs in the extremities. Adjacent bone change was a significant predictor of patient dissatisfaction.

Competing interest
The authors declare that they have no competing ineterset.

Authors' contribution
All authors read and approved the final manuscript.

Author details
[1]Department of Diagnostic and Interventional Radiology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka Suita, Osaka 565-0871, Japan. [2]Department of Orthopedic Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka Suita, Osaka 565-0871, Japan. [3]Department of Orthopedic Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakmichi Higashinari, Osaka 537-8511, Japan. [4]Department of Pediatric Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka Suita, Osaka 565-0871, Japan.

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Initial experience with use of hydrogel microcoils in embolization of pulmonary arteriovenous malformations

Keigo Osuga[1*], Kentaro Kishimoto[1], Kaishu Tanaka[1], Masahisa Nakamura[1], Yusuke Ono[1], Noboru Maeda[1], Hiroki Higashihara[1], Tetsuro Nakazawa[2] and Noriyuki Tomiyama[1]

Abstract

The purpose of this study is to describe our initial experience with embolization of pulmonary arteriovenous malformations (PAVMs) using hydrogel microcoils. The technical and radiological outcomes were retrospectively reviewed in seven patients with nine simple-type PAVMs (median feeder size 4 mm, range 3-6 mm) who underwent embolization. Hydrogel microcoils were mainly used, and detachable bare microcoils were combined as needed to occlude the terminal feeding artery just before the sac. Of a total of 43 microcoils, 30 (69.8%) hydrogel microcoils were deployed in eight PAVMs with the median number 3.5 (range 2 to 6) per lesion. All hydrogel microcoils were successfully deployed without microcatheter stuck or malposition. In the remaining one small PAVM, only soft bare microcoils were used, however, resulting in recanalization requiring additional coils in the second session. The venous sac was substantially shrunk in all lesions treated with hydrogel microcoils with the median size reduction rate 95.0% (range 81.8% to 99.0%) during the median follow-up period 10 months (range 6 to 18 months). In conclusion, hydrogel microcoils were safely and effectively applied for occluding PAVMs with relatively small feeders.

Keywords: Pulmonary arteriovenous malformations; Embolization; Hydrogel microcoils

Introduction

Pulmonary arteriovenous malformations (PAVMs) are abnormal fistulous connections between pulmonary arteries and veins forming a venous sac. PAVMs occur either sporadically or as a part of manifestations of hereditary hemorrhagic telangiectasia (HHT). The patients may suffer from stroke or brain abscess due to paradoxical embolism, dyspnea and fatigue due to hypoxemia, and rarely, hemoptysis or hemothorax due to spontaneous rupture of the venous sac. According to the international guidelines for the diagnosis and management of HHT, transcatheter embolization is the first-line treatment for symptomatic PAVMs (Faughnan et al. 2011). For asymptomatic PAVMs, the feeding artery 3 mm or greater in diameter is generally considered as the size threshold for embolization, although embolization can be also performed in smaller feeding arteries. Although efficacy and safety of coil embolization has been demonstrated in mostly case series, reperfusion of treated PAVMs mainly occur due to recanalization through the coils (Pollak et al. 2006). Therefore, it is important to increase the coil packing density to achieve high degree of cross-sectional occlusion for long-term occlusion (Pollak et al. 2006).

Recently, hydrogel coated detachable microcoils or hydrogel microcoils (Azur, Terumo, Tokyo, Japan) has been introduced for peripheral coil embolization (Nambiar et al. 2008). The hydrogel microcoils are coated with polymer that expand in contact with blood, and thus, have an advantage of greater filling volume compared with bare platinum coils. Although hydrogel microcoils theoretically lower the risk of recanalization, there have been few reports to describe details of their application in PAVM embolization. Therefore, the feasibility or role of hydrogel microcoils in this particular indication remains unclear. In this report, we describe our initial experience with use of hydrogel microcoils in a series of patients with PAVMs with relatively small feeding arteries.

* Correspondence: osuga@radiol.med.osaka-u.ac.jp
[1]Department of Diagnostic and Interventional Radiology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
Full list of author information is available at the end of the article

Materials and methods

Patients

We retrospectively reviewed the medical records and radiological findings of seven consecutive patients with a total of nine PAVMs who underwent embolization mainly using hydrogel microcoils between December 2012 and June 2013. All patients were female, and the mean age was 57.9 years old (range 24 - 69). One patient had hereditary hemorrhagic telangiectasia (HHT), according to the Curaçao's clinical diagnostic criteria (Shovlin et al. 2000). Six patients had a single PAVM, and one patient had three PAVMs. Four patients had past histories of neurological complications including brain infarction due to paradoxical embolism (n = 3) and spinal hemorrhage from spinal AVM (n = 1). All nine lesions consisted of a simple AV fistula with a single feeder and a single drainer. These feeding arteries were relatively small with the median diameter of 4 mm (range 3-6 mm). The median maximum size of venous sac was 13.5 mm (range 3 to 17 mm). Room air oxygen saturation was >95% in all patients, and none of them showed hypoxic symptoms. The indication for coil embolization included i) past history of paradoxical embolism (n = 3), ii) feeder size 3 mm or larger (n = 7), and/or iii) multiplicity (n = 1), that were considered as the further risks of paradoxical embolism. The written informed consent was obtained from in all patients, and this retrospective study was approved by the internal review board.

Coils

Hydrogel microcoils are 0.018-inch detachable platinum microcoils coated with hydrogel polymer that expand when the polymer contact with blood. The hydrogel expands approximately five times the original volume of the bare coil, thus may offer more filling volume with potentially fewer number of microcoils. The available coil size were 3 mm, 4 mm, 5 mm, 6 mm, and 8 mm in loop diameter and 5 cm, 10 cm, and 20 cm in the extended length. The hydrogel microcoils were prepared and deployed according to the manufacturer's instruction. For pre-softening, the stretched hydrogel microcoil was immersed in warm sterile saline at 60 degree C in five to ten seconds until the coil curls. When the hydrogel microcoil was appropriately positioned in the vessel, the coil was released with a detachment controller (V-Grip, Terumo, Tokyo, Japan). Repositioning time of the coil was limited within three minutes from the time of loading into the microcatheter, because it will become difficult to retract the coil once in contact with blood. It will take approximately 20 minutes until complete expansion of the hydrogel.

Embolization procedures

All procedures were performed under local anesthesia. A 6Fr introducer sheath was inserted via the right femoral vein in six patients and via the right jugular vein in one patient because of lower leg paralysis and atrophy as a sequel of spinal hemorrhage. Diagnostic pulmonary angiography was performed using a 4Fr pigtail catheter sequentially to each lung to identify all lesions and their feeding arteries. Then, the pigtail catheter was exchanged to a coaxial guiding catheter systems (Medikit, Tokyo, Japan) consisting of an outer 6Fr multipurpose guiding catheter and an inner 4Fr catheter with a short distal angle. Following the selective insertion of the inner coaxial catheter into the feeding artery, the outer guiding catheter was advanced over it to provide adequate support for coil deployment maneuvers. When the coaxial guiding catheter system was settled, a 2.0Fr two-marker microcatheter with inner diameter 0.022 inch (Progreatβ^3, Terumo, Tokyo, Japan) was coaxially advanced in the distal feeding artery as close to the venous sac as possible. As a rule, the terminal segment of the feeding artery beyond any significant normal branches was occluded with mainly hydrogel microcoils. Because of the limited reposition time of the hydrogel microcoil within three minutes, the attending nurse measured the time from the coil loading into the microcatheter, and called how much time was left per minute to complete the coil deployment. Softer bare platinum detachable microcoils (Helipaq or Cashmere, Codman & Shurtleff, Raynham, MA, USA) were combined as needed. For the first coil, an oversized coil was deployed to avoid coil migration into the pulmonary vein. If there was a small distal normal branch near the venous sac, the anchor technique was applied to secure the coil stability, where the initial few centimeters of the coil was hooked in the side branch and the rest of the coil was released in the feeding artery. Once the first coil was settled, hydrogel microcoils were mainly used for the filling of the feeding artery until the blood flow substantially reduced by test injection of contrast media. The hand injection angiography was sequentially obtained 10 minutes and 20 minutes after the last hydrogel microcoil was deployed. If there was residual blood flow even after 20 minutes, additional hydrogel coils or softer bare platinum microcoils were deployed as needed. Finally, adequate occlusion of the feeding artery was confirmed by the main pulmonary angiography, and it was also assessed if any accessory feeding artery was missed. Technical success was defined as complete occlusion of the targeted lesions at the end of procedure.

During the procedure, patients received prophylactic antibiotics with 1 g of intravenous cefazolin sodium. They also received 3,000 – 5,000 U of intravenous heparin to maintain the activated clotting time (ACT) beyond 200 seconds to avoid the thrombi formation around the catheters and coils that could cause paradoxical embolism before the complete occlusion was achieved.

Image assessment

Follow-up CT scans using 64-channel multi-detector CT scanners (LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA) were performed between 6 months and 18 months after the procedure to evaluate the shrinkage of venous sac and any coil-associated complication. The whole lung non-contrast CT images were obtained with a 0.625 mm collimation and 1.375 pitch. Efficacy of embolotherapy was assessed by the bi-dimensional size reduction rate of the venous sac at its longest diameter on the follow-up axial CT images in the lung window setting. The measurement of the venous sac was performed by consensus of the two board-certified diagnostic radiologists from authors.

Results

All embolization procedures were successfully completed. The technical and radiological results are summarized in Table 1. Of a total of 43 microcoils, 30 (69.8%) hyrdogel microcoils were deployed in eight PAVMs with the median number 3.5 (range 2 to 6) per lesion. All hydrogel microcoils were deployed within one to two minutes. Neither coil stuck in the microcatheter, malposition in the target vessel, nor migration into non-target vessels occurred. Exceptionally, in one small PAVM, only soft bare platinum microcoils were deployed because of the microcatheter instability in the small and tortuous feeding artery (Case 6, lesion no. 8). In five PAVMs, oversized bare platinum microcoils were combined for the first one or two coils to create a scaffold for the following hydrogel microcoils. In two PAVMs, small softer bare platinum microcoils were added proximal to the hydrogel microcoils. The ratio of number of hydrogel microcoils per total number of coils ranged from 42.9% to 100% with the median 70.9%. The ratio of total length of hydrogel microcoils per the total length of all coils ranged from 41.7% to 100% with the median 66.7%. Complete feeder occlusion was observed at 10 minutes in two lesions (25%), and at 20 minutes at three lesions (37.5%) (Figure 1). In the remaining three PAVMs (37.5%), additional hydrogel microcoils (n = 2) or softer bare platinum microcoils (n = 1) were added because of incomplete occlusion at 20 minutes.

In one patient with three PAVMs, the two lesions of the left lung and the one lesion of the right lung were treated in two separate sessions with two-months interval. In the second session, the left pulmonary angiography revealed that the lesion treated by hydrogel microcoils was completely occluded, whereas the other smaller lesion treated by bare microcoils alone showed recanalization of the feeding artery through the coil interstices (Figure 2). Therefore, small bare platinum microcoils were added proximal to the previous coils. The venous sac was substantially shrunk in all PAVMs treated with hydrogel coils. The median size reduction rate of venous sac was 95.0% (range 81.8 to 99.0%) during the median follow-up period 10 months (range 6 to 18 months). During the follow-up, no minor or major complication was observed in all patients.

Discussion

Transcatheter embolization has been the treatment of choice for occluding PAVMs. Fibered pushable coils have been widely used for the mechanical occlusion of feeding arteries (Pollak et al. 2006). Recently, the Amplatzer vascular plug (AVP) family has been also introduced to occlude large feeders safely with a single device or in combination with coils (Trerotola & Pyeritz 2010). On the other hand, the advance in microcoils and microcatheter technology has enabled selective embolization of small or tortuous vessels, where insertion of the regular delivery catheters is considered difficult or harmful. Especially, soft detachable microcoils, although they are expensive, have been increasingly applied in PAVM embolization, because they can be repositioned, offer more precise deployment,

Table 1 Summary of the technical and radiological results

Case no./ PAVM no.	Feeder diameter (mm)	No. of hydrogel microcoils (%)	Total length (cm) of hydrogel microcoils (%)	Loop size of hydrogel microcoils	Venous sac size (baseline)	Venous sac size (last follow-up)	Follow-up periods (months)	Size reduction rate (%)
1-1	6	6 / 6 (100)	60 (100)	8-3	14 × 10	7 × 1	12	95.0
2-2	5	4 / 6 (66.7)	40 (42.5)	6-3	17 × 10	4 × 2	6	95.3
3-3	3	3 / 4 (75.0)	25 (55.6)	4-3	3 × 3	1 × 1	6	88.9
4-4	4	5 / 5 (100)	60 (100)	6-3	16 × 12	2 × 1	6	99.0
5-5	3	2 / 3 (66.7)	40 (66.7)	4	14 × 9	3 × 2	14	95.2
6-6	4	3 / 7 (42.9)	60 (75.0)	6-4	13 × 7	3 × 2	11	93.4
6-7	3	3 / 7 (42.9)	30 (41.7)	4-3	11 × 6	4 × 3	9	81.8
6-8*	3	0 / 10 (0)	0 / 56 (0)	NA	8 × 5	4 × 3	9	70.0
7-9	5	4 / 5 (80)	60 (66.7)	4-3	11 × 10	2 × 2	6	96.4

* Only bare microcoils were used in two sessions. NA: not applicable.

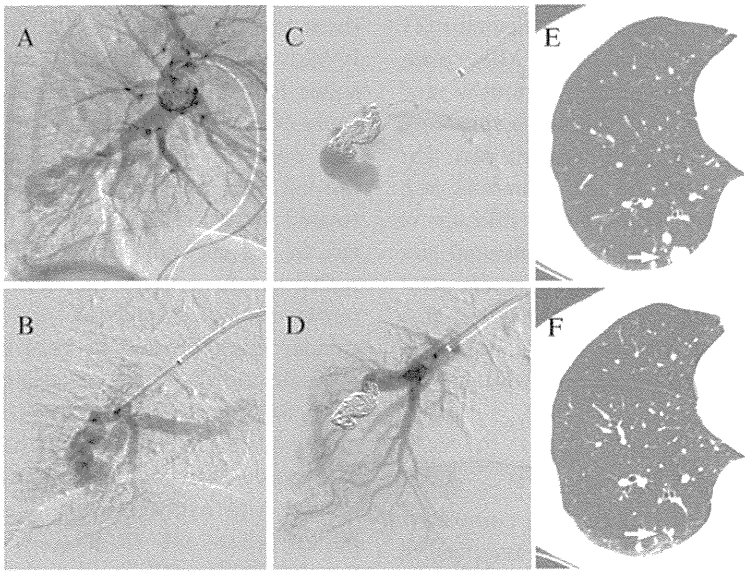

Figure 1 A 66 year-old woman with the right PAVM (Case 2). A. The pulmonary arteriogram (lateral projection) shows a simple type AVM of the posterior segment. **B**. The selective angiogram shows the tortuosity of the terminal feeding artery beyond the normal branch. **C**. A microcatheter was advanced as close to as possible to the sac. Following the two oversized 10 mm and 6 mm anchoring bare microcoils, four 6-3 mm hydrogel microcoils were deployed for filling a short segment of feeding artery. Immediately after embolization, a minimal flow remained in the venous sac. **D**. Post embolization angiogram at 20 minutes shows the complete PAVM occlusion. **E**. The baseline non-contrast CT image shows the venous sac on the posterior lung surface (arrow). **F**. The six-month follow-up CT image shows shrinkage of the venous sac (arrow).

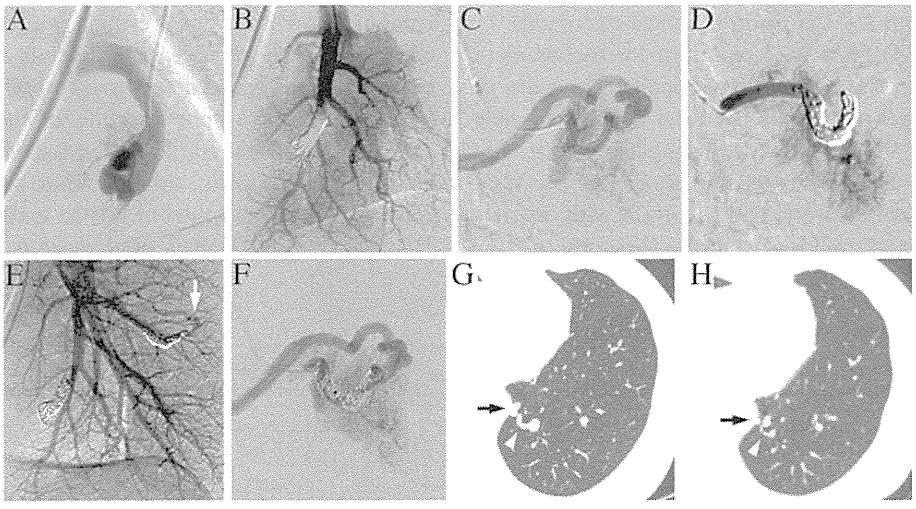

Figure 2 A 62 year-old woman with three PAVMs (Case 6). A. The selective angiogram shows the PAVM in the posterior segment. **B**. The distal feeding artery was embolized with three 6-4 mm hydrogel microcoils and four additional 3 mm bare platinum microcoils. **C**. Selective angiogram of the small PAVM in the superior segment shows the tortuosity of the distal feeding artery. **D**. Because of microcatheter instability, six 4-3 mm 0.014-inch bare detachable microcoils alone were deployed. Post embolization angiogram shows the feeding artery occlusion. **E**. After two months, the follow-up pulmonary arteriogram was obtained in the second session to treat the PAVM in the right lung (not shown). The PAVM in the posterior segment treated by hydrogel microcoils remained occluded, whereas the smaller PAVM in the superior segment treated by bare microcoils alone shows recanalization (arrow). **F**. Selective angiogram reveals the recanalization through the coil interstices. Four additional 3 mm bare microcoils were packed proximally to achieve complete occlusion (not shown). **G**. The baseline non-contrast CT image shows the venous sac (arrow) and the draining vein of the PAVM in the posterior segment (arrowhead). **H**. The eleven-month follow-up CT shows shrinkage of the venous sac (arrow) and normalization of the draining vein size (arrowhead).

and prevent systemic coil migration (Dinkel & Triller 2002; Greben et al. 2013). However, such soft and thin bare platinum detachable microcoils are susceptible for recanalization. Indeed, in our series, one small lesion treated by bare platinum microcoils alone showed early recanalization in two months. In the literatures, recanalization after successful embolization has been the main cause for reperfusion of PAVMs (Pollak et al. 2006; Milic et al. 2005). The reported recanalization rates were up to 20% of PAVMs treated with coils (Pollak et al. 2006; Milic et al. 2005) and 5 to 10% of PAVMs treated with AVPs (Trerotola & Pyeritz 2010; Fidelman et al. 2008), possibly through the coil interstices or plug meshes. The technical reason for recanalization may be inadequate cross-sectional occlusion with a fewer number of devices or those of inappropriate size than desired (Milic et al. 2005). Therefore, dense cross-sectional occlusion by filling the coil interstices is one of the solutions to enhance the packing density.

The main advantage of hydrogel microcoils is to increase the packing density by hydrogel expansion among the coil interstices and to establish tight mechanical vessel occlusion without the aid of thrombus formation. These features may be helpful in the embolization procedure like for PAVMs under systemic heparinization. However, there have been few reports describing application of hydrogel microcoils for PAVM embolization. In an early report of peripheral application of hydrogel microcoils, the coils were deployed through the existing coil mesh in a partially recanalized PAVM (Nambiar et al. 2008). The additional increase in volume after hydrogel swelling helped to achieve complete occlusion of the PAVM. In other reported indications, hydrogel microcoils reduced the coil numbers when compared with fibered microcoils in prophylactic embolization of the gastroduodenal artery before yttrium-90 radioembolization for liver cancers (Maleux et al. 2013). In another comparison study for intracranial aneurysms, the higher packing density, shorter total coil length, and lower recanalization rates were proven in the hydrogel microcoil group than in the bare coil group (White et al. 2011). The study suggested that hydrogel microcoils constitute at least 50% of the total coil length for <10 mm aneurysms, and at least two thirds of the total coil length for >10 mm aneurysms. In our series, the median proportion of hydrogel microcoils was 66.7% of the total coil length. However, there has been no report yet about the optimal proportion of hydrogel microcoils to decrease the recanalization rates of PAVMs. Although the significant sac shrinkage was obtained in our series in the short period up to eighteen months, longer-term follow-up is necessary to ensure the sac involution or freedom from symptoms, as reperfusion can occur in once resolved PAVMs even after more than two years (Milic et al. 2005).

There were some disadvantages in the hydrogel coils. We occasionally experienced slight resistance in the coil delivery, and the microcatheter kicking-back, although no coil resulted in the catheter stuck or malposition in the target vessel. Because of the relatively high coil rigidity, adequate support by a deeply inserted guiding catheter and the use of braided microcatheter was important for controlled delivery of the hydrogel microcoils. High-flow type microcatheters with inner-diameter 0.027 inch would be also helpful for better passage of the hydrogel microcoils. In addition, the limited reposition time within three minutes was stressful for operators, but all hydrogel microcoils could be deployed within two minutes that allowed one or two times attempts of coil reposition. In our early experience, we waited for full hydrogel expansion up to 20 minutes after the last hydrogel coil was deployed. The progressive vessel occlusion was observed in five of eight lesions even under systemic heparinization.

There are several limitations in our study. First, this is a retrospective short-term observational study with a small number of patients. Second, only 0.018-inch hydrogel microcoils were evaluated in PAVMs with relatively small feeding arteries, as 0.035-inch hydrogel coils were not yet available in our country. Third, contrast-enhanced CT scan was not performed in our series, thus reperfusion of PAVM could not be precisely assessed. However, the marked shrinkage of venous sac was good indicator for efficacy of embolization even on plain CT images. Forth, it still remains unclear if combining the hydrogel microcoils can reduce the total coil number or the recanalization rates in PAVM embolization. Cost-effectiveness should be also considered, as the hydrogel microcoils are more expensive than other coils in our country. Therefore, a further study would be necessary to prove the true advantage of combining hydrogel microcoils over conventional coils alone by a randomized controlled trial. For larger feeding arteries where the regular guiding-coaxial catheters are accessible, the terminal feeder occlusion using 0.035-inch fibered coils with or without combining AVPs may remain the suitable procedure.

In conclusion, the hydrogel microcoils were safely and effectively applied for occluding PAVMs with relatively small feeders. The substantial sac shrinkage was obtained in all treated PAVMs. Further study will be needed to confirm if hydrogel microcoils reduce the recanalization rates.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
KO performed all embolization procedures, and wrote the manuscript. KK helped imaging assessment and preparing the case-list table. KT, MN, YO, MN, HH, and TN were engaged in the clinical practices. NT supervised the study and gave advices. All authors read and approved the final manuscript.