

Use of Glubran 2 acrylic glue in interventional neuroradiology

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Abstract

Introduction Glubran 2 is a cyanoacrylate-based synthetic glue modified by the addition of a monomer synthesized by the manufacturer. With this material it is possible to obtain the stability of endovascular embolization that is needed to treat tumours and vascular disease.

Material and methods We report our 3-year experience of the use of Glubran 2 for treating extracerebral tumours, spinal tumours, spinal arteriovenous malformations, and brain and spine dural fistulae. Glubran 2 was diluted with Lipiodol and injected in a continuous column with the flow rate monitored by seriography. The injection was stopped when retrograde flow was displayed in the afferent vessel.

Results There were no periprocedural or subsequent clinical complications and the glue resulted in successful selective permanent occlusion with intralesional penetration similar to the angiographic features of microcatheterization.

Conclusions The embolization procedure was technically straightforward and relatively safe. However, Glubran 2 can be difficult to use and the procedure does carry major risks for patients. Glue injection requires in-depth study of the lesion, its circulation and the collateral circulation to avoid severe complications due to inappropriate use.

Keywords Glue · Guiding catheter · Embolization · Coaxial system · Tumour · Arteriovenous malformation · Fistula

Introduction

Glubran 2, a new class 3 glue, has been available for several years for internal and external surgical use and fulfils the rules laid down by European directive 93/42/EEC. It is a cyanoacrylate-based synthetic glue modified by the addition of a monomer synthesized by the manufacturer. Glubran 2 has a lower thermal polymerization temperature than other available cyanoacrylate preparations (around 45°C), a major factor limiting procedure-induced endothelial cell damage. The glue spreads through the circulation causing vessel occlusion, a strong inflammatory reaction in the vessel wall, endothelial cell injury and necrosis. In addition, the arterial occlusion caused by Glubran 2 has been shown to be stable at 30 and 60 days [1, 2].

The stability of endovascular embolization is very important both in treating tumours and vascular disease, unlike embolization using particles which provide temporary occlusion requiring rigid planning of embolization and surgery [3]. In addition, current en bloc resection techniques allow tumours to be removed in one session [4, 5]. Yet these techniques are not always applicable due to individual anatomical restrictions typical of the brain, skull base and spine, so that local and systemic disease control depends on complete intralesional excision. This type of surgery is often hampered by perioperative bleeding and embolization is a useful preliminary treatment and provides long-term palliation in inoperable cases.

Another prerequisite for selective embolization is control of glue injection of the vascular afferents feeding the lesion because of "hazardous" vascular shunts in the brain and spine/spinal cord regions. For this, the choice of embolizing agent and the injection technique used, are crucial.

The rationale behind the use of Glubran 2 lies in its potential to achieve permanent and more uniform occlusion

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of the pathological circulation than particles. This avoids rigid postembolization planning of surgical tumour resection and, if used as a definitive treatment, avoids craniotomy.

We report our 3-year experience of the interventional use of Glubran 2 at the Neuroradiology Service of Bellaria Hospital, Bologna, Italy, for the treatment of intracranial and spinal tumours, spinal arteriovenous malformations (AVM), and brain and spine dural fistulae [10–17].

Materials and methods

In all procedures the microcatheter was positioned as proximally as possible to the pathological circulation to achieve selective embolization. Glubran 2 (GEM, Viareggio, Italy) was injected after rinsing the microcatheter with glucose solution to remove saline flush solutions and blood. The glue was usually diluted with Lipiodol and injected in a continuous column with the flow rate monitored by serigraphy. The injection was stopped when retrograde flow was displayed in the afferent vessel. The Glubran 2/Lipiodol mixtures were prepared at concentration ratios of 1:1, 1:2 and 1:3 depending on the dilution required in each case.

Table 1 summarizes the procedures carried out from January 2001 to September 2003 with a breakdown of the diseases treated and the number of procedures.

Tumours

Brain

Ten patients with extra-axial intracranial tumours underwent presurgical embolization using Glubran 2 (Table 2).

Table 1 Interventional procedures from January 2001 to September 2003

	Location and pathology	Material	Patients treated	Procedures
Tumours	Brain	Glubran 2	10	15
	Spine/spinal cord	Glubran 2 + particles	22	43
Vascular disease	Brain AVM	Glubran 2 + Onyx	5	14
	Brain dural fistulae	Glubran 2 + Onyx + coils	5	16
	Spinal cord dural fistulae	Glubran 2 + coils	1	4

Six patients had a benign tumour (meningioma) and four malignant tumours (one sarcoma, two epidural metastasis and one intradural metastasis). Diagnostic angiography was performed in all patients with selective investigation of the internal and external carotid arteries and the vertebral artery. For embolization a microcatheter was positioned as close as possible to the vessels to be occluded and all procedures were performed with Glubran 2 mixed with Lipiodol as the sole embolizing agent. Five patients had only one selective microcatheterization carried out with Glubran 2 injection. Two patients (patients 6 and 7) had successful embolization of two afferents. Three patients (patients 1, 4 and 5) underwent several selective microcatheterization attempts, but only one injection was possible due to vessel tortuosity.

Spine/spinal cord

Twenty-two patients (11 males and 11 females) with spine/spinal cord expanding lesions were treated (Table 3). The lesions were characterized by spinal cord and root compression and high flow pathological circulation caused by steal from the spinal cord circulation. Nine of the patients had benign tumours (one aneurysmal cyst, two schwannomas, two haemangiomas, two osteoblastomas, one neurofibroma and one osteochondroma) and 13 malignant tumours (1 chordoma and 12 metastases). Tumour masses were located as follows: four cervical spine, nine dorsal, eight lumbar and one sacral. Patients with cervical tumours underwent angiographic investigation of the vertebral, ascending cervical, deep cervical arteries, thyrocervical arteries and external carotid arteries. In dorsolumbar lesions, the intercostal and/or lumbar arteries were examined at the level affected together with those of at least two levels above and below the lesion. In low lumbar lesions, the hypogastric arteries were catheterized in addition to the lowest lumbar arteries. Care was taken to identify the anterior spinal axis and possible significant perimedullary afferent arteries.

Embolization was performed using Glubran 2 and particles (Contour, Boston Scientific, Target Therapeutics, Fremont, Calif.; Embospheres, Biosphere Medicals, Roissy Charles de Gaulle, France) in 11 patients. In patient 11 (aneurysmal cyst) the mass enveloped the vertebral artery causing severe stenosis, and it was necessary to sacrifice the artery to ensure a radical surgical outcome. Since collateral blood flow was good, the vessel was occluded with two Gold Valve balloons (8×21).

In our experience, particles were confined to patients in whom stable catheterization was impossible and prior to glue embolization in order to create a preferential flow route for Glubran 2 and to reduce the circulation in large tumours with extensive pathological circulation.

Table 2 Brain tumours

Patient no.	Sex	Age (years)	Histotype	Material	No. of procedures	Complications	Surgery
1	M	55	Extradural metastasis	Glubran 2	One	No	Yes
2	F	65	Meningioma	Glubran 2	One	No	Yes
3	M	42	Intradural metastasis	Glubran 2	One	No	Yes
4	F	36	Meningioma	Glubran 2	Two (one failed due to vessel tortuosity)	No	Yes
5	M	65	Meningioma	Glubran 2	Two (one failed due to vessel tortuosity)	No	Yes
6	F	57	Sarcoma	Glubran 2	Two	No	Yes
7	M	58	Meningioma	Glubran 2	Two	No	Yes
8	M	62	Meningioma	Glubran 2	One	No	Yes
9	M	63	Meningioma	Glubran 2	One	No	Yes
10	F	26	Extradural metastasis	Glubran 2	One	No	Yes

Vascular diseases

Brain AVM

Five patients were treated with Glubran 2 (Table 4). Glubran 2 was used pure in one patient (patient 33), with a small nidus fed by a terminal branch of the pericallosal artery and early discharge into the superior sagittal sinus, to ensure immediate occlusion with protection of the venous

supply. A minimum amount (0.25 ml) was injected in this case.

In two patients (patients 36 and 37) Glubran 2 was mixed with Lipiodol and used as the only embolizing agent. In patient 36 with a complex arteriovenous malformation in the frontal horn of the lateral ventricle and in the genu of the corpus callosum with early drainage into a large tortuous vein draining into the vein of Galen, three embolizations were performed, but two failed due to the

Table 3 Spine/spinal cord tumours

Patient no.	Sex	Age (years)	Histopathological findings	Location	No. of procedures	Materials	Complications	Surgery
11	F	10	Aneurysmal cyst	Cervical	Four	Glubran 2, particles, balloons	No	Yes
12	F	25	Neurofibroma	Lumbar	Two	Glubran 2, particles	No	Yes
13	F	32	Schwannoma	Cervical	One	Glubran 2	No	Yes
14	M	49	Schwannoma	Dorsal	One	Glubran 2	No	Yes
15	M	46	Haemangioma	Dorsal	Two	Glubran 2, particles	No	Yes
16	M	43	Haemangioma	Dorsal	Four	Glubran 2, particles	No	Yes
17	M	30	Osteoblastoma	Lumbar	Two	Glubran 2, particles	No	Yes
18	M	51	Osteoblastoma	Cervical	Two	Glubran 2	No	Yes
19	M	30	Osteochondroma	Cervical	(Spontaneous occlusion)	-	No	Yes
20	F	70	Metastasis	Dorsal	Two	Glubran 2, particles	No	Yes
21	F	37	Metastasis	Lumbar	One	Glubran 2	No	Yes
22	F	35	Metastasis	Dorsal	Two	Glubran 2	No	Yes
23	M	58	Metastasis	Lumbar	One	Glubran 2	No	Yes
24	M	49	Metastasis	Lumbar	Four	Glubran 2, particles	No	Yes
25	M	67	Metastasis	Lumbar	One	Glubran 2, particles	No	Yes
26	M	70	Metastasis	Lumbar	Two	Glubran 2, particles	No	Yes
27	M	61	Metastasis	Dorsal/ lumbar	Five	Glubran 2, particles	No	Yes
28	F	65	Metastasis	Lumbar	Three	Glubran 2, particles	No	Yes
29	F	69	Metastasis	sacral	One	Glubran 2	No	Yes
30	F	68	Metastasis	Dorsal	Two	Glubran 2	No	Yes
31	F	55	Metastasis	Dorsal	(Failure)	-	No	Yes
32	F	65	Chordoma	Dorsal	Two	Glubran 2, particles	No	Yes

Table 4 Brain AVM

Patient no.	Sex	Age (years)	Location	No. of procedures	Material	Complications	Surgery
33	F	37	Frontal	One	Glubran 2	No	No
34	M	21	Parietal	Five	Glubran 2/Lipiodol, Onyx	Passage of a small bolus of Glubran 2 into the vein	No
35	F	37	Opercular	Seven	Glubran 2/Lipiodol, Onyx	Passage of a small bolus of Glubran 2 into the vein	No
36	M	34	Frontobasal	One	Glubran 2/Lipiodol	No	No
37	M	49	Frontal	One	Glubran 2/Lipiodol	Very delayed venous flow	Yes

angulation of the origin of Heubner's artery feeding the nidus and the scanty flow to the AVM. Only one procedure was undertaken in patient 37 which resulted in delayed blood flow to the draining vein.

Patient 34 had five embolization procedures, two with Glubran 2 and Lipiodol and three with Onyx (MTI, Irvine, California), an alternative liquid embolic material that can be injected in brain aneurysm or AVMs. Patient 35 had seven embolization procedures, two with Glubran 2 and Lipiodol and five with Onyx. When Glubran 2 was injected in both patients, a small amount of glue leaked into the draining vein, but no significant flow changes ensued.

Brain dural fistulae

Five dural fistulae were treated with Glubran 2 (Table 5). Glubran 2 was the sole embolizing agent in three patients (39, 41 and 42). GDC coils (Boston) were also inserted in patient 38, and Glubran 2, Onyx and coils (TruFill, Cordis) were positioned during different embolization sessions in patient 40. This last patient had a rete mirabile fistulous circulation anterior to the outflow of the jugular vein fed by branches of the vertebral arteries and external carotid artery. The fistulous circulation discharged into the transverse

sinus, and the contralateral jugular vein and the ipsilateral jugular vein were opacified only via cortical drainage vessels. The patient first underwent embolization of the arterial afferents via the arterial route and then coils were inserted via the venous route, and lastly the vertebral artery feeding the fistula was occluded with coils. The patient had a well-compensated contralateral circulation.

Spinal cord dural fistula

One patient with a low-flow fistula was treated with Glubran 2 (Table 6). The fistula was located in the small pelvis fed by branches of the internal iliac artery with venous drainage at the level of the spinal canal from D12 to L1. The patient underwent two embolization sessions but it proved difficult to reach the fistula. Two injections of a 1:1 mixture of Glubran 2 and Lipiodol were carried out followed by another session with insertion of GDC coils proximal to the fistulous branches. Embolization was incomplete as the fistula was still evident after the procedure, albeit with a delayed flow rate. The patient subsequently underwent surgery during which the coils proved an excellent reference point for the surgical approach.

Table 5 Brain dural fistulae

Patient no.	Sex	Age (years)	Location	No. of procedures	Materials	Complications	Surgery
38	M	58	Auricular artery, neuromeningeal trunk, jugular bulb	Three	Glubran 2/ Lipiodol, coils	No	No
39	F	61	Internal maxillary artery, carotid siphon, superficial draining veins	Two	Glubran 2/ Lipiodol	No	No
40	F	38	Vertebral artery, external carotid artery, jugular bulb	Five	Glubran 2/ Lipiodol coils, Onyx	No	No
41	M	59	Middle/posterior meningeal artery, occipital and auricular arteries, carotid siphon, large varicose venous drainage vessels to cortical veins, flowing into transverse sinus	One (two failed)	Glubran 2/ Lipiodol	No	No
42	F	69	Occipital, auricular and middle meningeal arteries, large cortical drainage vessels	Five	Glubran 2/ Lipiodol	No	No

Table 6 Spinal cord dural fistula

Patient no.	Sex	Age (years)	Location	No. of procedures	Materials	Complications	Surgery
43	M	66	D12–L1 low-flow arteriovenous fistula fed by a hypertrophic sacral branch originating from the iliac artery (fistula tip in small pelvis)	Four	Glubran 2/ Lipiodol, coils	No	Yes

Results

Tumours

In extra-axial intracranial tumours, embolization of accessible afferent vessels was complete. There were no clinical or technical complications and the procedures were well-tolerated by patients. In five patients CT scans after embolization displayed intralesional penetration of glue and its distribution. Glubran 2 was seen to penetrate the tumours, diffusing distally within the mass, a major requirement for permanent embolization. The subjective impression of neurosurgeons was positive with a significant reduction of perioperative bleeding compared to particle embolization undertaken previously (Fig. 1).

Embolization was a presurgical procedure in nine patients with benign primary spinal tumours. Glue embolization was cancelled in one of these patients (patient 19) since the afferent artery was found to be occluded at angiographic follow-up. Complete embolization was achieved in six procedures and partial embolization in two procedures (patients 13 and 18). In patient 13 the tumour was vascularized by several afferents and only the vessel allowing the most stable catheter placement was treated, and in patient 18 the anterior spinal artery was displayed in another tumour afferent. Among the malignant spinal tumours, complete devascularization of the tumour was achieved in 5 of 12 patients with good penetration of both

particles and glue into the pathological circulations. Embolization was technically successful in all patients without periprocedural complications and was judged to be highly satisfactory at subsequent surgery. Some patients reported a marked reduction of pain after the embolization procedure.

Vascular disease

The results obtained in treating cerebral vascular disease depended on whether treatment was definitive or a presurgical procedure.

Among the patients with AVM, patient 33, treated by injection of pure Glubran 2, showed no evidence of the malformation at angiographic follow-up. In two patients (patients 34 and 35) in whom a small amount of Glubran 2 leaked into the venous segment, no flow changes were recorded and the many embolization procedures performed disclosed almost complete occlusion of the nidus which was subsequently treated by radiosurgery. Surgery followed embolization in only one patient (patient 37). At the time of this report, further procedures were planned for patient 36.

There were no technical or periprocedural complications in any patients with dural fistulae, and embolization was the sole treatment. The latest angiographic follow-up failed to disclose signs of the fistulae in two patients (patients 38 and 39), and the lesion was stable without further vessel recruitment in another two patients (patients 40 and 41).

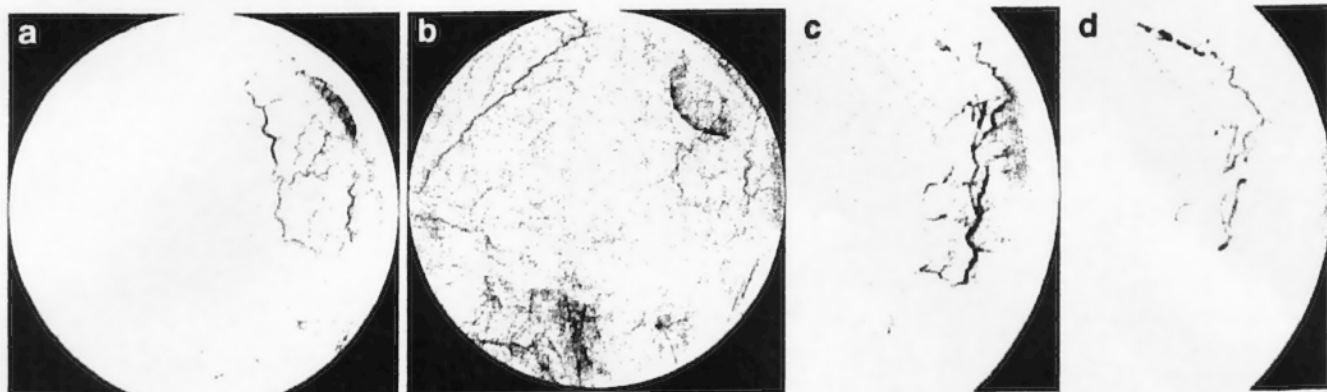


Fig. 1 Patient 10: extradural metastasis. **a, b** External carotid angiography in the arterial phase, anteroposterior view (**a**) and lateral view (**b**), shows pathological circulation feeding the tumour from the

middle meningeal artery. **c, d** Superselective angiography (**c**) and Glubran 2 injection (**d**) show diffusion within the pathological circulation

One patient (patient 42) had recurrence of the embolized fistula.

Discussion

Our experience using Glubran 2 for embolization of brain and spine/spinal cord tumours, AVM and dural fistulae highlighted the advantages and disadvantages of this new material.

The outcome of Glubran 2 embolization of tumours should be compared with the results of embolization using particles, the material most widely used [6–9]. Particles penetrate well within the lesion, are easy to handle and available in different sizes suitable for treating the different types of pathological circulation. However, particles have the disadvantage of making the embolization unstable with the possibility of lesion afferents recanalizing and in the short-term bleeding during subsequent surgery. Although small-calibre particles (50 μm) have the advantage of good intralesional penetration, they can lead to embolization of unplanned locations through shunts not visible on control angiography in intra- and extracranial locations or in the spinal cord. Larger particles (150–250 and 250–350 μm) are safer, but tend to aggregate causing more proximal embolization which facilitates the recruitment of collateral vessels to feed the tumour. Particle penetration may even be excessive, making a highly vascularized mass dry and brittle, thereby hampering subsequent en bloc resection of the lesion [3].

These disadvantages are overcome by the new embolizing agent Glubran 2 which being liquid diffuses throughout the vessel network, but this feature also makes glue injection more

challenging in less expert hands. Some steps can be taken to control the flow of injection. Firstly, the glue can be diluted with Lipiodol to adjust the mixture to the individual patient depending on morphological features and blood flow. Secondly, pressure and speed of injection can be varied in relation to high or low lesion flow.

In treating spine/spinal cord disease, when catheterization is stable it is helpful to occlude the arterial segment of the vessel with the guiding catheter to ensure good flow control and then inject the glue from the microcatheter into the main afferent vessel with arrested blood flow (Fig. 2) [18]. The resulting absence of blood flow will prevent polymerization of the glue allowing it to penetrate more distal intralesional branches. Occlusive catheterization of the metameric arteries does not lead to ischaemia in tissues fed by normal vessels given the numerous anastomoses in the circulation of the dorsal and ventral spine. In most of our patients, superselective microcatheterization was achieved and glue tended to diffuse into tumoral vessels especially in those with a highly vascularized pathological circulation.

In vascular diseases, the primary aim is to embolize the arterial afferents of AVM by an endovascular procedure and to occlude the fistulous communication. The wide variety of angiographic features encountered in brain AVM and dural fistulae preclude adoption of a standard procedure using a single embolizing agent. In AVMs with a nidus fed by many afferents which could be treated using an endovascular approach, Onyx was selected as the embolizing agent and injected in different embolization sessions (patients 34 and 35). Glubran 2 proved relatively safe when injected into a small AVM nidus or small portions of a nidus fed by very small vessels with a stable catheter position. Excellent

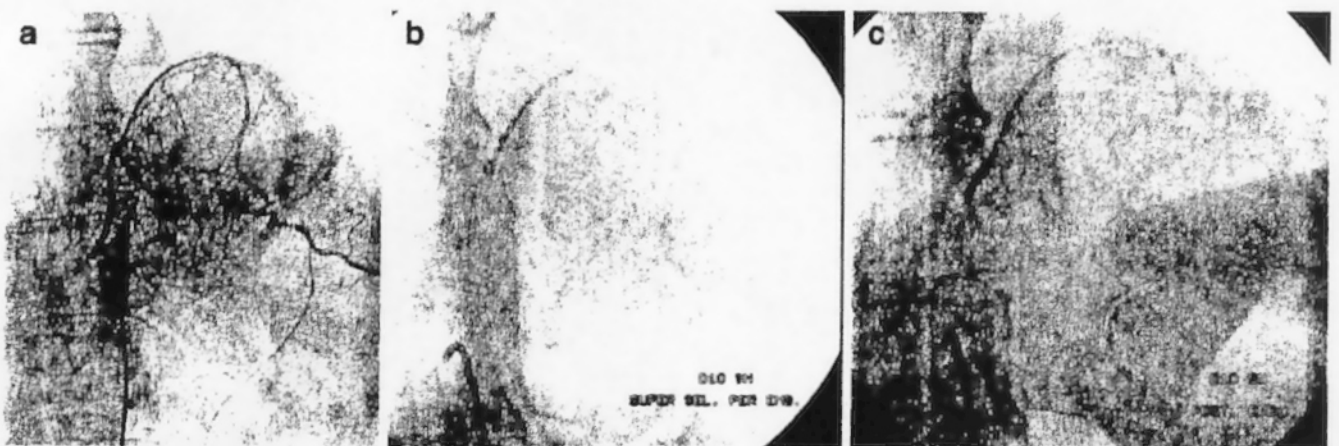


Fig. 2 Patient 14: D10 schwannoma. **a** A lesion highly vascularized by the ipsilateral metamer artery. **b** Catheterization of the D10 metamer artery using a coaxial microcatheter with occlusion of the origin of the metamer artery with the tip of the guiding catheter.

c Glubran 2 injection after stopping the washing flow from the guiding catheter. Note the cast of the glue that was confined to the arch of the tumour mass with occlusion of the afferents

glue penetration was achieved in these cases due to the glue's high fluidity, yielding images similar to those following contrast medium injection during superselective catheterization. One of the major difficulties in using acrylic glue to treat AVMs is possible leakage into draining veins. A minimal amount of Glubran 2 leaked into the venous segment in two procedures (patients 34 and 35), but probably because of a high rate of blood flow, the glue adhered to the venous wall without causing significant slowing of venous drainage.

The choice of arterial or venous or dual arterial and venous approaches for embolization of brain dural fistulae was the primary decision. In our experience, the majority of lesions were treated using Glubran 2 alone, but other materials, such as coils (patient 38) and coils with Onyx (patient 40), were sometimes used. Coils were used where fistulous branches arising from larger arterial pedicles were present to prevent Glubran 2 spreading to other arterial territories or to close an artery ipsilateral to the fistula if it was the sole feed to the fistulous branches (Fig. 3).

Conclusions

Glubran 2 is an officially approved acrylic glue for endovascular use. Previous animal studies have shown some of the advantages of Glubran 2 such as less damage to surrounding tissue combined with excellent intralumenal penetration.

In our department Glubran 2 has been used in tumoral and vascular pathology, and has been shown to be an excellent embolizing agent. The embolization procedure is technically straightforward and relatively safe. Using Glubran 2 in hypervascularized tumours and in vascular disease, we have demonstrate some of its main advantages and how it can be used. The advantages of Glubran 2 include the injection of a uniform mixture, adjustable only in concentration, and the control of flow, making it an ideal material in the endovascular treatment of different brain and spine/spinal cord diseases. However, Glubran 2 can be difficult to use and the procedure does carry major risks for

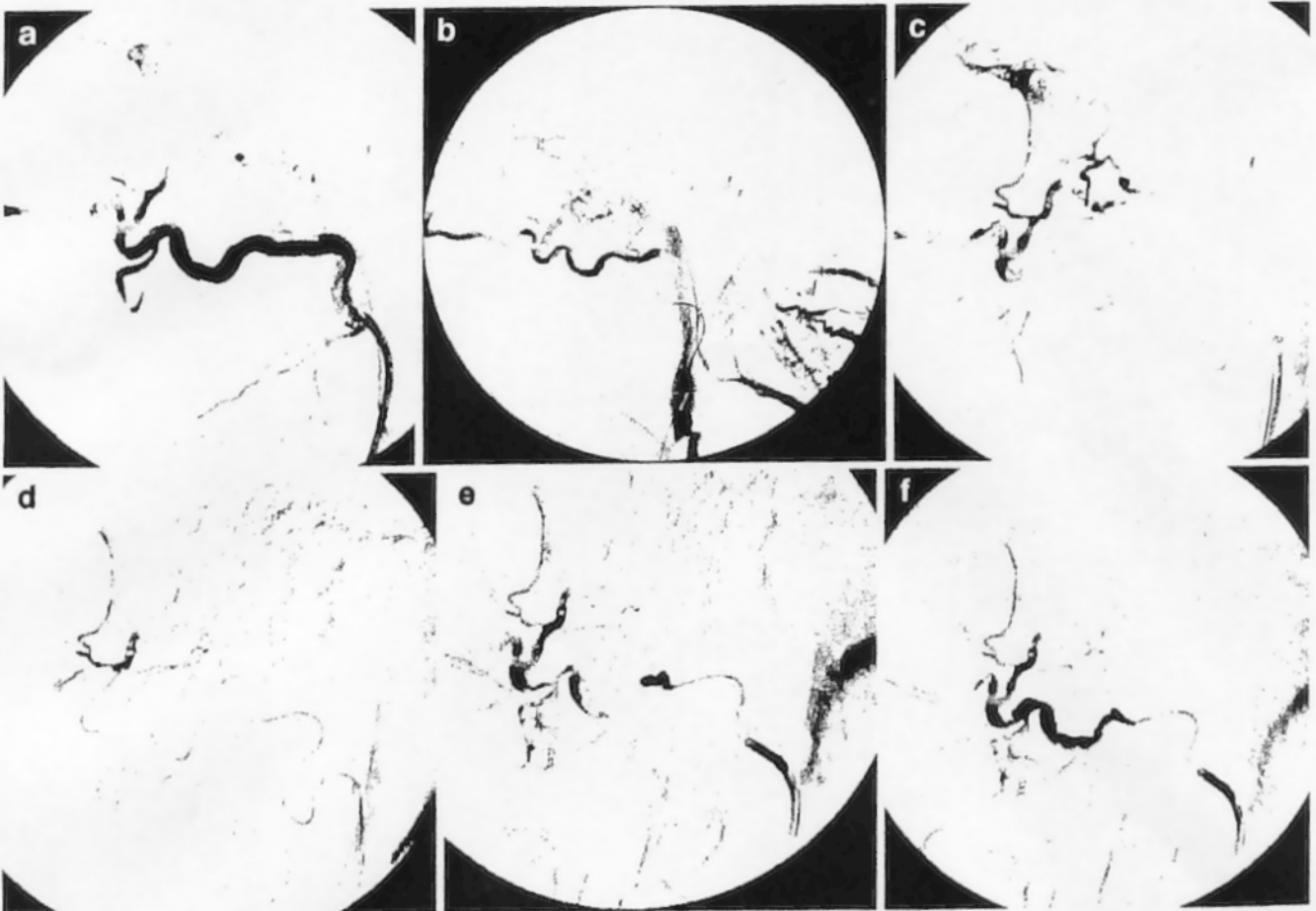


Fig. 3 Patient 38: dural fistula. **a** Digital angiography of the occipital branch of the external carotid artery, lateral view. Distal and proximal afferent branches from the occipital artery feed the fistula. **b** Early visualization of the jugular vein. **c** Digital angiography showing coaxial catheterization distal to the origin of the afferent branches and occlusion of the occipital artery with coils. **d** Superselective

catheterization of the distal branch to the fistula and injection of Glubran 2. Note the diffusion of Glubran 2 in the feeder with the protection of the occipital artery. **e, f** Glubran 2 injection at a more proximal position to the microcatheter with occlusion of the proximal branch

patients. Glue injection requires in-depth study of the lesion, its circulation and the collateral circulation to avoid severe complications due to inappropriate spread.

Further study is needed to investigate the characteristics of different embolizing agents in individual situations and surgeons should be prepared to use a combination of different materials.

Conflict of interest statement We declare that we have no conflict of interest.

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