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Surgical Outcome of Cerebral Aneurysm Clipping Treated with Immunosuppressants: Report of 11 Cases and Review of the Literature

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Abstract

There are no reports on the outcomes of clippings in patients who receive immunosuppressants, for example, due to connective tissue diseases or following organ transplantation. We thoroughly reviewed these cases focusing on the perioperative management phase. The study included 11 patients with intracranial aneurysms who were taking immunosuppressants; between 2007 and 2014. We performed 12 clipping surgeries. Their clinical records were reviewed for age and gender, aneurysms' location and size, perioperative management of the immunosuppressive drugs, and surgical complications. The study included nine females and two males, aged between 52 and 71 years (mean 60.1 ± 8.5 years). The clinical presentation in five cases was subarachnoid hemorrhage (SAH); the aneurysm was incidentally diagnosed in six patients (7 aneurysms). The reasons for taking immunosuppressants were autoimmune disorder in nine patients and liver transplantation in two patients. Daily intake of oral immunosuppressants for the patients with liver transplantation was discontinued for 2–4 days, and no infectious complications were evidenced. The weekly course of immunosuppressive drugs for the patients with autoimmune disorder was continued in eight of nine patients. Caution must be exercised when considering the suitability of clipping for patients taking immunosuppressants, but surgery outcomes are generally favorable; when operative treatment is required, we believe it to be comparatively safe, if the perioperative management is conducted in close collaboration with the relevant departments.

Key words: cerebral aneurysms, clipping, immunosuppressants, organ transplantation, autoimmune disorders.

Introduction

The incidence of intracranial aneurysm and subarachnoid hemorrhage (SAH) may be higher in patients with various connective tissue diseases, especially in those with systemic lupus erythematosus (SLE).[1–4] Moreover, organ transplantation is sometimes performed in the cases of liver and/or kidney disease, including cases of polycystic liver and/or kidney disease, in which complications such as cerebral aneurysms are known to occur.[5,6] Additionally, patients receiving immunosuppressants, for either their autoimmune disease or after organ transplantation require cerebral aneurysm clipping. However, the outcome of both clipping surgeries and perioperative management of these drugs remain unclear. This study presents 11 patients who underwent clipping and received immunosuppressants. We thoroughly reviewed these cases focusing on the perioperative management phase.

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Materials and Methods

The study was approved by the Institutional Review Board, and the need for informed consent was waived because of the retrospective nature of this study. The study included 11 patients with intracranial aneurysms who were taking immunosuppressants; between 2007 and 2014, we performed 12 clipping surgeries. The immunosuppressants used in this study included cyclophosphamide (CPA), mycophenolate mofetil (MMF), cyclosporine (CsA), tacrolimus (FK), and methotrexate (MTX). Although MTX was originally an anti-cancer drug and not an immunosuppressant in the strictest sense of the word, it is widely used to treat rheumatoid arthritis (RA) because of its immunosuppressive

effects. Therefore, MTX was also included as an immunosuppressant in this study.

We performed 218 clipping surgeries and 44 coil embolizations for cerebral aneurysms between 2007 and 2014. Three patients who underwent clipping had Sjogren's syndrome but were not taking immunosuppressants. None of the patients who underwent coil embolization were on immunosuppressants. Decisions on whether an aneurysm was suitable for endovascular treatment were made only after a discussion between the neurovascular surgeons and a neuroradiologist. The choice of modality was mainly based on the overall complex architecture of the aneurysm (wide neck, large size, or incorporated vessel origins), and not on the patient's age or SAH grade. The standard approach to unruptured aneurysms in our hospital is to intervene in aneurysms exceeding 5 mm and to observe those under 5 mm. Intervention is also recommended for aneurysms with documented growth.

The patients included in this study received a standard dose of prophylactic Cephem antibiotics perioperatively.

Their clinical records were reviewed for age and gender, aneurysms' location and size, perioperative management of the immunosuppressive drugs, and surgical complications. The patients presenting temporary or permanent neurological deterioration and/or patients who underwent additional surgical therapy were considered if any surgical complications.

Results

A summary of the cases is presented in Table 1. The study included nine females and two males, aged between 52 and 71 years (mean 60.1 ± 8.5 years). The clinical presentation in five cases was SAH; the aneurysm was incidentally diagnosed in six patients (7 aneurysms). The aneurysm locations were as follows: two were on the internal carotid artery (ICA); five on the middle cerebral artery (MCA) bifurcation; four on the anterior communicating (A-com); two on the distal anterior cerebral artery (dACA); and one on the vertebral artery (VA). The reasons for taking immunosuppressants were autoimmune disorder in nine patients and liver transplantation in two patients. Daily intake of oral immunosuppressants for the patients with liver transplantation was discontinued for 2–4 days, and no infectious complications were evidenced. The weekly course of immunosuppressive drugs for the patients with autoimmune disorder was continued in eight of nine patients. MTX was discontinued for single patient (Case 3) presenting with severe SAH (WFNS grade 5), who had origin-unknown high fever (FUO), considering reduced joint load in the bed-ridden state.

Surgical complications were noted in four patients: transient cerebral ischemia in two (spasm after SAH in 1, and venous infarction in 1), cerebrospinal fluid leakage in one, and status epilepticus in one. Except for the WFNS grade 5 SAH patients (Case 3), there was no patient with worsening of modified Rankin Scale (mRS) of more than 2. The representative cases (Case 5 and 7) are described below.

[***Case 5***] A 66-year-old female patient underwent coil embolization of unruptured MCA aneurysm at another hospital 12 years ago; she was followed up by regular neuro-radiological examinations. She had RA also and medicated steroid history. Five years ago, her RA condition worsened, and started receiving immunosuppressant (MTX). A de novo aneurysm (2 mm) at the posterior communicating artery at its origin (IC–PC) was detected 2 years ago by three-dimensional computed tomographic angiography (3D-CTA), and the follow-up radiological examination confirmed the growth of aneurysm (4 mm). Therefore, the clipping was planned after the cessation of MTX at the hospital. However, the operation was canceled due to uncontrolled systematic inflammation after cessation of immunosuppressant. Further, the patient was admitted to our hospital for the control of RA and clipping surgery. Magnetic resonance angiography (MRA), and 3D-CTA demonstrated no recurrence of left MCA aneurysm after coil embolization and a de novo left IC-PC aneurysm (Figs. 1A and 1B). After her RA condition was controlled by receiving immunosuppressant (MTX 8 mg/week), the patients underwent clipping surgery. During the surgery, we could squarely confirm no recurrence of left MCA aneurysm after coil embolization (Fig. 1D), and then we performed complete clipping (Figs. 1E and 1F). Post-operative 3D-CTA demonstrated no recurrence of left MCA aneurysm after coil embolization and complete clipping (Fig. 1C). The postoperative course was uneventful, and she was discharged with no neurological deteriorations.

[**Case 7**] A 57-year-old female was performed living-donor liver transplantation for primary biliary cirrhosis (PBC) 4 years ago, and had been receiving immunosuppressants to prevent rejection episodes. She was presented right numbness 6 months ago, with MRI and MRA showing left thalamic infarction and unruptured A-com aneurysm (5 mm). She hoped the clipping surgery will prevent aneurysm rupture. After consultation with the doctors who prescribed the immunosuppressive drugs FK 4 mg/day, mycophenclate mofetil (MMF) 1000 mg/day, predonisolone (PSL) 5 mg/day), they concluded that cessation for a few days would not be dangerous. Therefore, we

Table 1 Summary of clinical data in the 11 patients included in this study

Case number	Age/ Sex	WFNS grade	Location	Disease for taking immunosuppressant	Immunosuppressant	Perioperative management	Complications
			Size	Past History	Steroid		Outcome
1	64 F	1	MCA 10 mm	RA (HL, smoking)	MTX (4 mg/week) PSL (5 mg/day)	cessation (-) steroid cover	transient dysarthria due to spasm Good (mRS0)
2	52 F	1	MCA 4 mm	SLE, RA (HT, DM)	CPA (750 mg/ months) PSL (20 mg/day)	cessation (-) steroid cover	none Good (mRS0)
3	71 F	5	A-com 8 mm	RA (HT)	MTX (6 mg/week) PSL (5 mg/day)	discontinue (MTX) steroid cover	pneumonia, hydrocephalus Poor (mRS5)
4	57 M	1	IC-anch 6 mm	RA (HL, smoking)	MTX (15 mg/week) PSL (5 mg/day)	cessation (-) steroid cover	none Good (mRS0)
5	66 F	1	A-com 4 mm	RA (HT, DM, HL)	MTX (6 mg/week)	cessation (-)	vitreous hemorrhage Good (mRS1)
6	56 F	unruptured	MCA 10 mm	Myopathy (HT)	FK (2 mg/day) PSL (20 mg/day)	cessation for 2 days steroid cover	none Good (mRS0)
7	57 F	unruptured	A-com 5 mm	PBC (after living-donor liver transplantation) HT, DM, HL, cerebral infarction	FK (4 mg/day), MMF (1000 mg/day) PSL (5 mg/day)	cessation for 4 days steroid cover	cerebrospinal fluid leakage Good (mRS0)
8	58 F	unruptured	A-com 8 mm	RA (DM, HL, cerebellar AVM)	MTX (10 mg/week)	cessation (-)	none Good (mRS0)
9	43 M	unruptured	MCA 3 mm	SLE (HT)	CsA (200 mg/day) PSL (12 mg/day)	cessation (-) steroid cover	transient aphasia due to venous infarction Good (mRS0)
10	66 F	unruptured	IC–PC 4 mm	RA (unruptured intracranial aneurysm (MCA))	MTX (8 mg/week)	cessation (-)	none Good (mRS0)
11	71 F	unruptured	MCA 8 mm	PBC (after living-donor liver transplantation)	FK (8 mg/day), MMF (1000 mg/day)	cessation for 3 days	seizure Good (mRS0)
		unruptured	VA-PICA 8 mm		FK (8 mg/day), MMF (1000 mg/day)	cessation for 2 days	none Good (mRS0)

A-com: anterior communicating artery, CPA: cyclophosphamide, CsA: cyclosporin, DM: diabetes mellitus, F: female, FK: tacrolimus, HL: hyper lipidemia, HT: hypertension, IC-anch: internal carotid artery-anterior choroidal artery, IC-PC: internal carotid artery-posterior communicating artery, M: male, MCA: middle cerebral artery, MMF: mycophenolate mofetil, MTX: methotrexate, PBC: primary biliary cirrhossis, PSL: prednisolone, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus.

performed clipping under steroid cover during surgery and cessation of immunosuppressants for 4 days. Although she suffered cerebrospinal fluid leakage, she was discharged with no neurological deteriorations.

Discussions

There are no reports on the outcomes of clippings in patients who receive immunosuppressants, for example, due to connective tissue diseases or following organ transplantation. Here, we present 12 cases of clippings in 11 patients. The patients' daily oral immunosuppressants were withdrawn for several days, while administration of weekly medications was continued uninterrupted throughout the perioperative period. The outcomes were largely favorable. To date, there are no similar reports and thus we believe this report is extremely valuable.

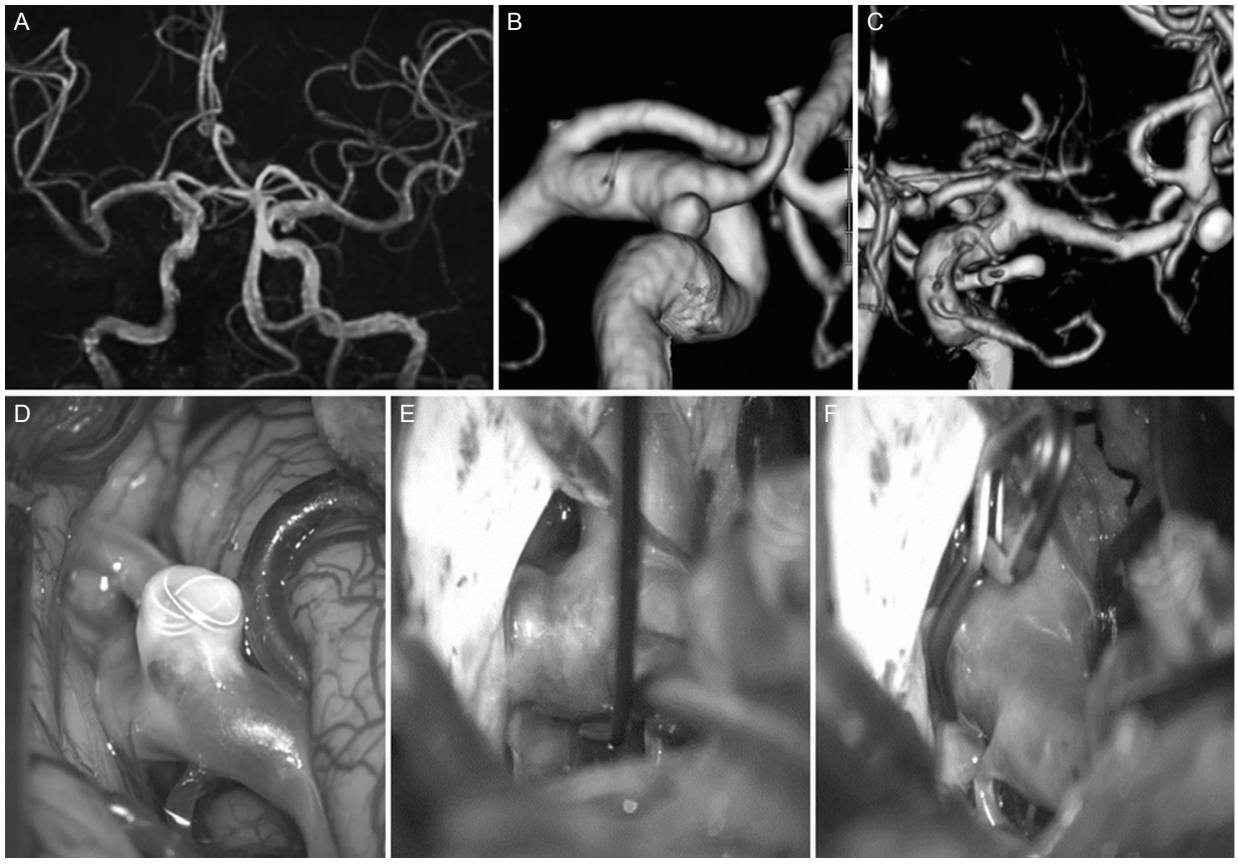

Fig. 1 Case 5. (A) Magnetic resonance angiography (MRA) demonstrated no recurrence of left middle cerebral artery (MCA) aneurysm after coil embolization and a de novo left internal carotid artery-posterior communicating artery (IC-PC) aneurysm. (B) Three-dimensional computed tomographic angiography (3D-CTA) demonstrated a left IC-PC broad neck aneurysm. (C) Postoperative 3D-CTA confirmed no recurrence of left MCA aneurysm and complete clipping. (D) Intraoperative photographs of the MCA aneurysm 12 years after coil embolization confirmed no recurrence of left MCA aneurysm. (E-F), Intraoperative photographs of the IC-PC aneurysm before (E) and after (F) clipping.

As previously mentioned, there are reports suggesting a relationship between autoimmune disorders and cerebral aneurysms,[1–4] and there is a possibility that for example inflammation of the vascular walls participates in the development of aneurysms.[7,8] There are a few reports of clippings in patients taking immunosuppressants due to autoimmune disorders,[9–12] but none describes the immunosuppressant administration methods in detail. There are a large number of reports on orthopedic surgery in patients with rheumatic diseases, in particular on artificial joints and immunosuppressants,[13–15] While for these patients steroids increase postoperative infections in a dose-dependent manner, the current consensus within orthopedic surgery is that treatment may be continued, as doses of MTX of 12.5 mg/week or lower do not lead to an increase in the postoperative infections.[13–15] Nothing can be said with absolute certainty, as there are no large-scale clinical studies on clippings. For the cases presented here, we carried out perioperative drug administration in a similar manner to the current consensus within the orthopedic surgery field, that is, we essentially performed the operations with medications uninterrupted. For scheduled surgeries, we considered MTX immunosuppressant doses in the up to 12.5 mg/week range to be within the realm of possibility, even if the doses were increased. We considered it appropriate to decrease steroids during the surgery; however, we believe one should refrain from excessive withdrawals or dose reductions such as those done by the previous physician for Case 5, as these may lead to a deterioration of the patient's condition.

As a standard for organ recipients, it is a common practice for hospitals to confirm that there are no major disorders in any of the main organs of the body before surgery. Furthermore, it is widely known that cerebral aneurysms are often associated with

polycystic kidney disease,[5,6] For these reasons, proactive screening is sometimes performed and the discoveries of cerebral aneurysms are not uncommon. Cerebral aneurysms discovered prior to transplantation are generally treated before transplantation.[16–18] In such cases, when an aneurysm is simultaneously discovered and shown to have enlarged upon follow-up, and when arteriosclerotic diseases develop after organ transplantation, treatment after organ transplantation may also be considered.[19] While there are no reports of clippings in patients taking immunosuppressants following organ transplantation, there are some reports in the cardiovascular surgery field.[20,21] Continuous administration of oral immunosuppressants is indispensable to prevent organ rejection after organ transplantation. While organ rejection is an immune response via the lymphocytes (primarily T-cells),[22] there is theoretically improbable that organ rejection will happen after a few days of immunosuppressants cessation. Furthermore, the number of bacterial infections complications is decreasing since long-term dosages after organ transplantation are fundamentally kept to a minimum, and reductions in neutrophilic function are insignificant thanks to advances in immunosuppressants.[23–25] Thus, perioperative infections are similar to those in normal postoperative patients, it is said that infections that develop postoperatively can easily become serious,[23–25] and therefore care must be taken. Based on the above, we believe it is appropriate to interrupt treatment with oral immunosuppressants following organ transplantation for a few days, until oral intake is possible. The actual treatments in the cases presented here were managed in such a manner, with no particular complications arising. It is important to note that there are many drugs that are contraindicated for concomitant use or that alter blood levels such as macrolide antibiotics, anti-epileptic drugs, and proton pump inhibitor. It is necessary to keep a close watch on the perioperative management by cooperating with the relevant departments.

With regard to antibiotics, there are no extant systematic reports on perioperative antibiotic therapy in neurosurgical patients receiving immunosuppressants. Several reports on orthopedic surgery in patients with rheumatic diseases report that standard antibiotic regimes do not increase the rate of postoperative infections.[13–15] While we should be careful about perioperative infections in patients taking immunosuppressants following organ transplantation, there are no reports that overdose or long-term administration of antibiotics reduces postoperative infections. Rather, it is believed that antibiotic therapy for these patients should be based on their liver or renal function.[23–25] Therefore, the patients on immunosuppressant in our study received the standard dose of antibiotics. They did not demonstrate any evidence of postoperative infections.

Finally, none of the patients who received coil embolizations in the study period were on immunosuppressive therapy. Although the reason for choosing clipping was mainly based on the overall complex architecture of the aneurysm, recent progress in neuro-endovascular procedures has made various complex aneurysms more treatable.[26] Although the patients on immunosuppressant in our study did not demonstrate any evidence of postoperative infections, this small case series study cannot assure safety of clipping for immunosuppressive patients. Therefore, coil embolization is a very promising technique for managing aneurysms in patients taking immunosuppressants, and can be considered as the first-line approach in these cases.

In conclusion, caution must be exercised when considering the suitability of clipping for patients taking immunosuppressants, but surgery outcomes are generally favorable; when operative treatment is required, we believe it to be comparatively safe, if the perioperative management is conducted in close collaboration with the relevant departments.

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Conflicts of Interest Disclosure

The authors have no financial or institutional interest. All authors have registered online Self-reported Conflicts of Interest (COI) Disclosure Statement Forms through the website for the Japan Neurosurgical Society members. We certify that this manuscript has not been published and is not being submitted for publication. This manuscript has been read and agreed for submission by all of authors.

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