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Churg-Strauss Syndrome: The Clinical Features and Long-term Follow-up of 17 Patients

Churg-Strauss syndrome (CSS) is a rare multi-system vasculitis; some cases have been reported in Korea. The aim of this study is to describe the clinical features, treatment outcome, and long-term follow-up of CSS from a single Korean medical center. Between 1995 and 2004, seventeen patients were diagnosed with CSS at the Department of Medicine of the Samsung Medical Center, Sungkyunkwan University School of Medicine. The diagnosis of CSS is based on the classification criteria of the American Collage of Rheumatology. All patients had asthma. As in other case series, the lung, peripheral nervous system, and skin were the most commonly involved organs. During the active stage of the disease, most of the patients exhibited peripheral blood eosinophilia and an elevated serum eosinophil cationic protein level. Ten patients were treated with pulses of methylprednisolone followed by tapering and cyclophosphamide, and the others were treated with corticosteroids alone. The outcomes after long-term follow-up were generally good. One patient who was refractory to initial treatment died of heart failure during the follow-up period. CSS was highly variable in its presentation and course. The manifestations may range from mild symptoms to life-threatening conditions. The outcome after long-term follow-up was as good as that of previous studies.

Key Words : *Churg-Strauss Syndrome; Treatment Outcome; Follow-up Studies*

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INTRODUCTION

Churg-Strauss syndrome (CSS) is a necrotizing systemic vasculitis which affects the small- to medium-sized blood vessels and is characterized by asthma, eosinophilia and extravascular eosinophilic granulomas (1). This disorder occurs in all age groups but has been reported most commonly in the third to fifth decades of life. The mean estimated incidence has been reported to be 2.4-6.8/1,000,000 in the general population, and 64.4/1,000,000 in asthma patients (2, 3). The prevalence is 13/1,000,000 in the general population, compared with 33/1,000,000 for polyarteritis nodosa (PAN) and 53/1,000,000 for Wegener's granulomatosis (WG) (4).

Most of previous reports regarding CSS in Korea have been case reports (5-8). Although the effect of intravenous pulse cyclophosphamide (CPM) in the treatment of CSS with refractory neuropathy to high-dose steroid treatment was reported (9), there have been no large single center studies of CSS patients reported in Korea.

The presentation and course of CSS are highly variable; manifestations may range from mild (asthma, sinusitis, cutaneous lesions) to life-threatening conditions (severe gastrointestinal [GI] involvement, heart failure, disabling neuropathy). Furthermore, diagnosis of CSS can be difficult because the manifestations vary with the disease stage. CSS is manifested in three consecutive phases: a prodromal phase consisting of allergic manifestations; a second phase of peripheral blood eosinophilia and eosinophilic tissue infiltrates; and a third phase consisting of vasculitic systemic manifestations (10). Treatment delay in the vasculitic phase may lead to irreversible major organ damage.

Here, we described 17 patients with CSS diagnosed at our Department of Medicine between 1995 and 2004. We analyze the clinical features, responsiveness to treatment, and long-term outcome.

MATERIALS AND METHODS

Subjects

Seventeen patients with CSS were selected from the Department of Medicine of the Samsung Medical Center, Sungkyunkwan University School of Medicine, between 1995 and 2004. Clinical data were obtained from outpatient and/or inpatient medical records.

The diagnosis was made when four or more of the American College of Rheumatology classification criteria were ful-

filled. These criteria include asthma, peripheral blood eosinophilia (>10% on differential white blood cell count), mononeuropathy or polyneuropathy, pulmonary infiltrates, paranasal sinus abnormality, and a biopsy finding containing a blood vessel with extravascular eosinophils.

Asthma was diagnosed on the basis of symptoms, measurements of reversibility of lung function abnormalities, and airway hyperresponsiveness by methacholine bronchoprovocation test.

Peripheral neuropathy consisted of mononeuropathy including mononeuritis multiplex and polyneuropathy. Central nervous system (CNS) involvement was considered when central neurologic manifestations occurred and could not be attributed to metabolic disorders or stroke.

Myocardial involvement was considered to be due to CSS when cardiac insufficiency occurred in the absence of preexistent risk factors such as coronary heart disease, valvular disease, hypertension, diabetes, and toxic or infectious agents and/or when histologically proven by examination of a myocardial biopsy.

GI involvement was considered when unexplained abdominal pain, intestinal bleeding, intestinal perforation, cholecystitis or pancreatitis was present without other pathogenic explanation.

Renal involvement was defined as the presence of unexplained increase in serum creatinine, proteinuria >1 g/day, abnormal urinary sediment and/or histologic findings in a renal biopsy consistent with systemic vasculitis.

The therapeutic regimen

In cases of severe, life-threatening, multi-system involvement (e.g., heart failure, severe GI involvement or disabling neuropathy), the patient treated with pulses of methylprednisolone followed by tapering and CPM. Intravenous pulses of CPM (500-750 mg/m^2) were administered at a total of six pulses at one-month interval. Depending on the clinical status of the patient, further pulses could be administered. At 2 weeks after every pulse CPM, routine blood tests were performed to examine cytopenia and presence or absence of liver and renal dysfunction. For maintenance therapy, low-dose prednisolone was orally administered according to the clinical manifestations and results of laboratory testing.

A patient was considered to be in remission when the clinical manifestations disappeared for a period of at least 6 months. However, neurologic sequelae could persist. A relapse was defined as the recurrence of clinical manifestations of CSS other than asthma or isolated eosinophilia.

RESULTS

Demographic data

Between 1995 and 2004, 17 patients (9 men, 8 women) were diagnosed with CSS in our department. The mean age at the time of diagnosis was 36.7 (range from 24 to 53) yr. The patients were followed for a mean period of 42.5 (range

Table 1. Clinical and laboratory features in 17 patients with Churg-Strauss syndrome

Case	Sex	Age (yr)	Time lapse BA-CSS (yr)	Involved organs	Laboratory findings				Treatment	Follow-up periods (months)
					PB eosinophil (/μL)	ECP (ng/mL)	ESR (mm/hr)	ANCA		
1	F	53	15	N, S	7,875	118	15	-	CS+CPM	46
2	M	28	18	L, S	2,436	492	25	-	CS	57
3*	F	39	3	L, S	378	72.2	32	-	CS	53
4	F	40	5	L, G	2,983	NC	2	-	CS	36
5	M	37	3	N, S	4,712	342	16	-	CS+CPM	85
6	F	50	10	N, S	310	339	27	-	CS+CPM	89
7	M	29	1	L, N, G, C	1,876	NC	77	-	CS+CPM	21
8	F	40	3	N, S	12,350	NC	33	-	CS+CPM	113
9	F	43	2	N, S	1,776	1,490	25	+ p-ANCA	CS+CPM	79
10	M	24	1	L, N	5,250	66.3	2	-	CS+CPM	27
11	M	50	10	L, N, C	5,100	86.5	6	-	CS+CPM	26
12	M	32	4	L, N, S, G	2,133	78.4	57	-	CS+CPM	26
13	M	28	6	L, N	13,940	40.7	49	-	CS	19
14	F	25	4	L	8,930	215	48	-	CS	14
15	M	29	2	L, S	5,050	NC	39	-	CS	12
16	F	26	0	S, C	6,920	181	28	-	CS	11
17	M	51	1	L, N	4,430	114	60	-	CS+CPM	8
Mean±SD		36.7±10.0	5.18±5.15		5085.2±3906.7	279.6±388.2	31.2±21.8			42.5±32.0

BA, bronchial asthma; CSS, Churg-Strauss syndrome; PB, peripheral blood; ECP, eosinophil cationic protein; ESR, erythrocyte sedimentation rate; ANCA, anti-neutrophil cytoplasmic antibodies; L, lung; N, nervous system; S, skin; G, gastrointestinal system; C, cardiovascular system; NC, not checked; p, perinuclear; CS, corticosteroids; CPM, cyclophosphamide. *These cases were already undergoing treatment with corticosteroids. Data are expressed as Mean±SD.

tremities. Skin biopsies were performed in 9 patients. Vasculitis was found in 6 biopsies, eosinophil infiltrates in 2 biopsies, and lymphocyte infiltrates in 1 biopsy.

GI involvement was seen in 3 patients (17.6%). In the first case (case 4) with recurrent epigastric pain, hemorrhagic gastritis was found on gastroendoscopy. In the second case (case 7), which presented with diarrhea, hemorrhagic erosions were found on colonoscopy and, on mesenteric angiography, thrombosis was found in the inferior mesenteric vein. In the third case (case 12) with severe acute abdominal pain, emergency laparotomy was performed and revealed peritonitis and perforation of the small intestine. Intestinal biopsy in the third case showed ulcer with granulation tissue, congested vessels, and mixed infiltration of inflammatory cells with a predominance of eosinophils.

Three patients (17.6%) presented with congestive heart failure with 2 patients showing a small amount of pericardial effusion (Table 4). A case 16, young woman was treated with corticosteroids alone with consideration of the possibility of pregnancy; the other 2 patients were treated with corticosteroids and CPM. A case 16 underwent coronary angiography with endomyocardial biopsy. No evidence of coronary artery disease was detected, but hypokinesia of the apex and anterolateral wall was noted. Histology showed focal myocarditis with prominent interstitial eosinophilic infiltration without vasculitis.

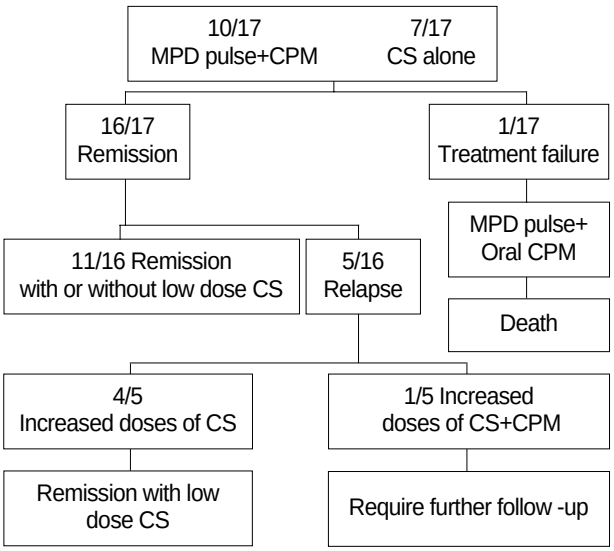

Fig. 1. Therapeutic modalities and disease course of 17 patients with Churg-Strauss syndrome. MPD, methylprednisolone; CPM, cyclophosphamide; CS, corticosteroids.

Laboratory findings

At the time of diagnosis, peripheral blood eosinophilia was present in 15 patients. Those without blood eosinophilia were already undergoing treatment with corticosteroids. The mean blood eosinophil count of all patients was 5085.2/μL (reference value <500/μL). Eosinophil cationic protein (ECP) level was checked in the sera of 13 patients, all of whom exhibited elevated serum ECP level at the time of diagnosis; the mean value was 279.6 ng/mL (reference value<16 ng/mL). Antineutrophil cytoplasmic antibodies (ANCA) were tested in all patients and myeloperoxidase-ANCA were detected in 1 patient at the time of diagnosis.

Table 5. Comparison of data from the present study with data from previous studies

	Chumbley et al. (17) (1950-1974)	Lanham et al. (10) (1976-1982)	Guillevin et al. (16) (1963-1995)	Solans et al. (15) (1977-1999)	Della Rossa et al. (14) (1989-2000)	Present study (1995-2004)
Type of study	Single center retrospective	Single center retrospective	Single center prospective	Single center retrospective/ prospective	Single center retrospective	Single center retrospective
No. of patients	30	16	96	32	19	17
M/F ratio	2.3	3	0.88	0.3	0.9	1.1
Mean age (yr)	47	38	48.2	42.5	46	36.7
Age range (yr)	15-69	ND	14-74	17-85	24-78	25-53
Clinical manifestations (%)						
Asthma	100	100	100	100	100	100
Generalized symptoms	ND	87	70.8	68.8	89.4	76.5
Pulmonary infiltrates	26.7	75	37.5	53.1	58	64.7
Peripheral nervous system	63.3	75	78	68	57.8	64.7
Skin	66.7	69	51	68.8	63	58.8
Gastrointestinal	16.7	56	33	37.5	47.3	17.6
Heart	16.7	25	35.4	28.1	31	17.6
Kidney	0.3	50	26	12.5	21	0
ESR	high	high	high	high	high	high
Eosinophilia	present	present	present	present	present	present
ANCA (%)	NC	NC	38	77	35	5.9

ESR, erythrocyte sedimentation rate; ANCA, anti-neutrophil cytoplasmic antibodies; ND, not documented; NC, not checked.

Disease course and long-term follow-up

Fig. 1 summarizes the therapeutic modalities and disease course of 17 patients with CSS.

Ten patients were treated with pulses of methylprednisolone followed by tapering and CPM. The other patients were treated with corticosteroids alone. Nine patients were administered on average 7.3 intravenous pulses of CPM; one patient was administered oral CPM. The serious adverse effects of CPM, such as hemorrhagic cystitis, bone marrow suppression, and neoplasm, were not documented during the follow-up period. One patient was refractory to the initial treatment and was subsequently placed on alternative pulses of methylprednisolone and oral CPM, but the patient did not comply with the treatment regimen and eventually died of heart failure. Five patients suffered relapses during the follow-up period and the clinical manifestations noted at the time of relapse were similar to those at the time of diagnosis. A suspected triggering factor for the relapses was the rapid tapering or discontinuation of corticosteroids treatment in 4 patients. At the time of the last visit, 13 of the 16 survivors in this study still required low doses of oral prednisolone (mean dose of 7.4 mg/day), 2 patients sustained remission without corticosteroids, and 1 patient required further follow-up.

DISCUSSION

CSS is a rare disorder characterized by eosinophilia and systemic vasculitis and almost invariably occurs in patients with asthma. Vasculitis commonly affects the lung, peripheral nerves, skin, heart, and GI tract. Renal involvement is not a necessarily characteristic of this disease, but it may occur in some cases (11).

The clinical spectrum of PAN or microscopic polyangiitis is similar to that of CSS, but the patients with PAN have no asthma, eosinophilia, or history of atopy. Additionally, patients with PAN have a higher frequency of nephritis, bowel vasculitis, and hypertension than do patients with CSS (12). The differentiation of these diseases may be important because CSS has a better rate of long-term remission than PAN when corticosteroid treatment was introduced (12, 13).

This is the first study to observe the clinical characteristics of CSS patients based on Korean experience in a single center over a 10-yr period. Table 5 shows data from the present study in comparison with those from previous studies.

The mean age of patients at disease onset was a little younger than that documented in previous studies (10, 14-17). The clinical and laboratory features seen in the present study was similar to that in the largest previous studies except that renal involvement and ANCA were demonstrated less frequently (10, 14-17).

As in previous studies, asthma was present in all the study patients and preceded CSS development in all patients but one, in whom asthma began simultaneously with CSS. A pulmonary infiltrates was present in 64.7% of patients. The most frequent findings of HRCT were consolidations in patchy or diffuse distribution and bronchial wall thickening. Worthy et al. (18) reviewed the HRCT findings in 17 patients with CSS. The most common abnormality consisted of bilateral consolidation or ground-glass attenuation in either patchy or predominantly peripheral distribution. Choi et al. (19) reviewed the HRCT findings in 9 patients with CSS. The most common findings included bilateral ground-glass opacities, centrilobular nodules mostly within the ground-glass opacities, and bronchial wall thickening.

Peripheral nerve involvement, present in 64.7% of patients, was the most frequent manifestation; its frequency in the present study was comparable to those seen in previous studies. Also as in previous studies, mononeuritis multiplex constituted the most frequent manifestation of peripheral nerve involvement and the peroneal nerve was the most frequently involved (20-22). All patients responded well to corticosteroids and CPM therapy, although 4 patients had residual symptoms, such as hypesthesia or neuropathic pain, sometimes associated with mild motor deficit. However, the symptoms were not severe in any of these cases. No involvement of the CNS was noted in the study subjects. CNS involvement may include palsies of the cranial nerves, cerebral hemorrhage or infarction, convulsions, and psychosis, but these occurrences are atypical. When CNS involvement dose occur with CSS, it causes significant morbidity and mortality (10, 23).

Skin involvement was present in 58.8% of patients, with palpable purpura presenting as the most frequent manifestation, as in previous studies (10, 14-17).

GI involvement was less frequent than in previous studies. Pathophysiology of GI involvement in CSS is known ischemic change from vasculitis and bowel wall infiltration with eosinophils (24). Churg and Strauss (1) described 12 of 13 patients with CSS with abdominal pain or diarrhea, one of whom died of intestinal perforation from ulceration. GI involvement in CSS, such as abdominal pain, diarrhea, intestinal bleeding, and intestinal obstruction was present in 37-62% of patients, as reported by other authors (10, 16, 17, 25).

In 17.6% of patients, cardiac manifestation was present. A case 16 showed striking improvement in left ventricular function (LVEF 54%) with improvement of hypokinesia on initial treatment. A case 11 relapsed at the eighth month and responded to increased doses of corticosteroids with conservative management, but case 7 was refractory to treatment and died of heart failure. Cardiac involvement includes eosinophilic endomyocarditis, coronary vasculitis, valvular heart disease, congestive heart failure, hypertension, and pericarditis (1, 11, 23, 26). In previously reported cases, treatment ranged from relatively high doses of corticosteroids to low doses combined with digoxin and diuretics. However, when immunosuppressive agents, especially CPM, were added to the treatment, it was found to be effective and to improve the

Table 2. Histologic findings in biopsies of the 14 patients with Churg-Struass syndrome

Biopsy site	No.	Vasculitis (No.)	Eosinophil infiltration without vasculitis (No.)	Other findings (No.)
Skin	9	6	2	1
Nerve	7	6	0	1
Lung	5	1	4	0
Pleura	1	0	1	0
Myocardium	1	0	1	0
Jejunum	1	0	1	0
Total	24	13	9	2

Table 4. Electrocardiography and echocardiogram in 3 Churg-Strauss syndrome patients with heart involvement

Case	ECG	Echocardiogram
7	RBBB	Focal thickness of endocardium, LVEF 35-40%, minimal pericardial effusion
11	VPC RAE	Enlargement of the chambers, LVEF 22%, moderate mitral regurgitation
16	RBBB	Global hypokinesia with RWMA, LVEF 30-35%, mild pericardial effusion

ECG, electrocardiography; RBBB, right bundle branch block; LVEF, left ventricle ejection fraction; VPC, ventricular premature complex; RAE, right atrial enlargement; RWMA, regional wall motion abnormality.

from 8 to 113) months.

Clinical features and histologic findings

Clinical and laboratory features of 17 patients with CSS are listed in Table 1 and the histologic findings in biopsies of 14 patients with CSS are detailed in Table 2.

Non-specific symptoms consisting of malaise, weight loss, fever, and arthromyalgia marked the early stages of vasculitis in 13 of 17 patients (76.5%).

All patients had asthma. The mean time lapse between the appearance of asthma and the onset of vasculitis was 5.18 (range from 0 to 18) yr. In 15 patients, asthma began when the patient was an adult (mean age 32.4 yr). Two patients had recent-onset asthma of less than 6 months, 1 of whom had asthma as presenting symptom of CSS. In 8 of 17 patients (47.1%), asthma was severe and had necessitated oral corticosteroids frequently. Mechanical ventilation was needed for status asthmaticus at the presentation of CSS in 1 patient. The upper respiratory tract was affected in 11 patients (64.7%). These patients complained rhinorrhea, nasal obstruction, and postnasal drip; sinusitis was demonstrated in paranasal sinus radiography. Three of these patients required endoscopic sinus surgery. The lower respiratory tract was also affected in 11 patients (64.7%). Transient pulmonary infiltrates were detected by chest radiography or high-resolution computed tomography (HRCT) scan. The infiltrates were various such as nodules, ground glass opacities, consolidations, and bronchial wall thickening in patchy or diffuse distribution with no preferred location. Three patients had hemoptysis. Alveolar hemorrhage was detected by the findings of bronchoalveolar lavage in 2 patients and 1 patient presented with acute respiratory failure. One patient had polymorphonuclear cell-dominant exudative pleural effusion and the finding upon pleural biopsy was mesothelial hyperplasia with infiltration of numerous eosinophils and plasma cells. Transbronchial lung biopsies or video-assisted thoracoscopic biopsies were performed in 5 patients. Eosinophilic vasculitis was found in 1 biopsy and vascular and interstitial eosinophil infiltrates were found in 4 biopsies

Table 3. Clinical features and electrodiagnostic findings in 11 Churg-Strauss syndrome patients with peripheral nerve involvement

Case	Symptom		Symptom distribution	NCS finding
	Sensory	Motor		
1	pain	foot drop	BU (d), BL (d)	distal poly neuropathy
5	tingling, numbness		BU (d)	mononeuropathy
6	pain, numbness	hand grip weakness, foot drop	RU (d), LL (d)	mononeuritis multiplex
7	pain, numbness	foot drop	BL (d)	mononeuritis multiplex
8	tingling, numbness	hand grip weakness, foot drop	RU (d), BL (d)	mononeuritis multiplex
9	tingling	hand grip weakness, foot drop	BU (d), BL (d)	mononeuritis multiplex
10	tingling, numbness		BL (d)	mononeuropathy
11	pain	foot drop	BL (d)	distal poly neuropathy
12	tingling	hand grip weakness	RU (d), LL (p)	mononeuropathy
13	numbness		RL (d)	mononeuritis multiplex
17	pain, numbness	foot drop	BU (d), BL (d)	mononeuritis multiplex

NCS, nerve conduction study; RU, right upper extremity; RL, right lower extremity; LL, left lower extremity; BU, both upper extremity; BL, both lower extremity; d, distal; p, proximal.

Eleven patients (64.7%) showed signs of peripheral nerve involvement without involvement of the CNS (Table 3). This manifestation was asymmetric and distal-dominant fashion. Electroneurography revealed mononeuritis multiplex most commonly. The most frequently involved nerve was the peroneal nerve, followed by tibial, sural, median, and ulnar nerves. Sural nerve biopsies were performed in 7 of 11 patients. Six showed vasculitis (one with fibrinoid necrosis, five with perivascular infiltrates) and the other showed axonal degeneration without vasculitis.

Ten patients (58.8%) experienced cutaneous manifestations: palpable purpura, papules, urticarial rash, vesicles, aseptic pustules, and Raynaud phenomenon. This manifestation typically involves the distal limbs, most frequently the lower ex-

prognosis (15).

Renal involvement was absent in our patients. Although it has been reported in CSS with variation across studies (0.3-67%) (10, 12, 14-17), unlike other necrotizing vasculitis such as WG or microscopic polyangiitis, renal failure is rare (11).

A total of 24 biopsies were performed in 14 patients. Three patients did not undergo any biopsy because of typical clinical manifestation. Vasculitis was seen in 6 of 9 skin biopsies (66.7%) and 6 of 7 nerve biopsies (85.7%). Therefore, the skin and nerves seem to be useful as diagnostic biopsy sites.

Corticosteroids have been the cornerstone of treatment for CSS since Chumbley et al. (17) reported a 5-yr survival rate of 62% and a median survival of more than 9 yr after early administration of corticosteroids. With acute multi-organ involvement or poor predicted prognosis, treatment with 15 mg/kg intravenous methylprednisolone for 3 days followed by 40-60 mg of prednisolone daily with gradual taper, has been advocated (27-29). However, administration of high dose corticosteroids for a long period has been known to complicate treatment-related side effects. Immunosuppressive agents such as immunoglobulin (30) or interferon (31) have been added to the treatment of patients with severe multi-organ involvement, unresponsiveness to corticosteroids, or relapse. CPM, in particular, has improved prognosis and has been recommended as adjuvant therapy in these patients (11, 29, 32). The benefit of pulse intravenous administration of CPM versus oral CPM is debatable. A small clinical study of 25 patients with CSS compared daily oral CPM with monthly intravenous CPM. The efficacy was comparable in both groups and the side effect profile was twice as great in the group receiving oral administration; the researchers in this study recommended pulse intravenous therapy over daily oral therapy for CSS (33). In very severe cases of CSS, corticosteroids and CPM may be insufficient to induce remission. In these cases, anti-TNF blocking agents such as infliximab or etanercept, may be added for a limited period of time (34).

In the present study, initial clinical remission was achieved in 16 patients (94.1%) and one patient (5.9%) died during follow-up. Five patients (29.4%) suffered single relapse and no suffered multiple relapses. The outcome in the present study was similar to that in recent reports (14-16).

In conclusion, the main difference in manifestation of CSS in this study compared to that in the previous studies was the absence of renal involvement and lower detection rate for ANCA. The question of whether renal involvement and ANCA are less present in Korean CSS patients needs to be answered by in a large study. Additionally, favorable treatment outcome in this study certainly needs further long-term study.

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