



Prevalence and Clinicoradiological Profiles of Respiratory Dysfunction in Patients with Medullary Infarction: Retrospective Case Study and Review of Literature

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Authors' contributions

This work was carried out in collaboration between all authors. Author KI designed the study with authors MS, TT, KM and TK. Authors MS, TT, KM and TK were performed the collection and analysis of clinico-radiological data. Author KI wrote the first draft of the manuscript and literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Respiratory dysfunction occurs in stroke patients. Little is known about the prevalence, clinical features and lesion topography in patients with dyspnea due to medullary infarction (MI). We aimed to evaluate the frequency and the clinicoradiological profile in dyspnic MI patients.

Methods: We serially reviewed clinical records and magnetic resonance imaging (MRI) findings in 2144 inpatients (1211 men and 933 women) with acute ischemic stroke from 2007 to 2013. The clinicoradiological features were studied in MI patients with respiratory dysfunction. The prevalence of dyspnic MI was estimated among patients with cerebral infarction or MI. Patients with extensive

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infarction in the brainstem or the posterior circulation area, and cerebral hernia were excluded.

Results: Ninety-five patients (47 men and 48 women) were diagnosed as MI. Six patients (2 men and 4 women) developed respiratory dysfunction. The prevalence was 6.3% (4.3% in men and 8.3% in women) in MI patients, and 0.3% (0.2% in men and 0.4% in women) in patients with cerebral infarction. Age was ranged from 38 to 78 years and the mean age (SD) was 70.0 (22.3) years. Abnormal respiration patterns included hyperventilation in 4 patients, dyspnea in one and apnea in one. Initial neurological examination revealed absent pharyngeal reflex and soft palatal palsy in all patients. Cough syncope, hiccup, dysphagia, circulatory failure, sensory deficits or dysuria was present simultaneously in several patients. MRI disclosed three types of lesion topography: 1) The bilateral medial and the right tegmental regions in the upper and the middle medulla oblongata, 2) The right-predominant extensive regions in the lower medulla oblongata, and 3) The left lateral and tegmental regions in the lower medulla oblongata. Magnetic resonance angiography or cerebral angiography showed severe degree of atherosclerosis, dural arteriovenous fistula or dissection in the vertebral artery. The prognosis was fatal in 2 patients, poor in 2 patients, and recovered in each one patient with and without intervention.

Conclusion: The present study indicated that the prevalence of dyspnic MI was 0.3% in ischemic stroke patients and 6.3% in MI patients. The neurological profile suggested cough, hiccup, circulatory instability, absent pharyngeal reflex, soft palatal palsy and dysuria. Lesion topography disclosed the tegmentum in unilateral or bilateral MI. Atherothrombotic mechanism and circulatory failure might predict high mortality.

Keywords: Medullary infarction; respiratory dysfunction; neurological profile; lesion topography; arterial pathogenesis.

1. INTRODUCTION

Medullary infarction (MI) is an uncommon disorder among patients with cerebral infarction, and the frequency of MI has been reported as approximate 1-4% in acute ischemic stroke [1-3]. Respiratory failure plays a crucial role in the prognosis of stroke patients. Occasionally, MI could induce dysfunction of both automatic and voluntary respiration [4,5] or failure of voluntary respiratory control with preserved automaticity [6,7]. Little is known about the prevalence, the neurological finding and the radiological topography in MI patients with respiratory disturbance. Here we aimed to elucidate the frequency and the clinicoradiological profile in patients with dyspnic MI.

2. PATIENTS AND METHODS

2.1 Study Patients

We reviewed clinical records and radiological findings of magnetic resonance imaging (MRI) and angiography (MRA) in 2244 consecutive inpatients (1261 men and 953 women) with acute ischemic stroke from 2007 to 2013. The clinicoradiological features were examined in MI patients with respiratory dysfunction. The frequency of these patients was estimated among patients with cerebral infarction and MI, respectively. Patients with extensive infarction in the brainstem or the posterior circulation area, and cerebral hernia were excluded from this

study. The present study was approved by ethical committee of Toho University Omori Medical Center.

2.2 Radiological Assessment

Brain MRI and MRA was produced by a 1.5-tesla superconducting system. MRI contained diffusion weighted, apparent diffusion coefficient map, T1-weighted, T2-weighted and fluid-attenuated inversion recovery images. Topography of MI was divided into the following 8 areas of the medulla oblongata; the upper, the middle and the lower level on cranio-caudal axis, and the lateral, the medial, the ventral, the tegmental and the dorsal region on transverse axis. Two experienced neurologists and one neuroradiologist reviewed brain MRI and MRA in all patients.

2.3 Clinical Assessment

The Clinical records of all participants were reviewed retrospectively for age, sex, usual cardiovascular disease (CVD) risk factors and vital signs.

3. RESULTS

3.1 Prevalence and Clinical Profile of MI Patients with Respiratory Dysfunction

Seventy patients (50 men and 20 women) with artificial pacemakers were excluded from the

present study because MRI and MRA were not performed. Finally, clinical and neuro-radiological data were reviewed in 2144 patients (1211 men and 933 women). Among 2144 patients (1211 men and 933 women) with acute ischemic stroke, 95 patients (47 men and 48 women) were diagnosed as MI. Six patients (2 men and 4 women) developed respiratory dysfunction. The prevalence was 6.3% (4.3% in men and 8.3% in women) in MI patients, and 0.3% (0.2% in men and 0.4% in women) in patients with ischemic stroke.

These demographic data are summarized in Table 1. The patient age was ranged from 38 to 78 years and the mean age (SD) was 70.0 (22.3) years. The first neurological examination revealed absent pharyngeal reflex and mild to moderate degree of soft palatal palsy in all patients. In addition to respiratory dysfunction, cough syncope, hiccup, circulatory failure, dysphagia, sensory deficits or dysuria was present. Abnormal respiration patterns included hyperventilation in 4 patients, dyspnea in one patient and apnea in one patient. All patients developed respiratory dysfunction during awaking and/or sleeping time at the same day of MI onset.

CVD risk analyses revealed hypertension in 5 patients, smoking in 2 patients and arrhythmia in one patient. The prognosis of dyspnic MI was fatal in 2 patients. Their cause of death was recurrent MI. Two patients showed poor prognosis. Remaining two patients had good recovery. One patient was treated with vascular intervention and another patient improved naturally.

3.2 Radiological Profile of MI Patients with Respiratory Dysfunction

Lesion topography is shown in Fig. 1.

Four patients had unilateral MI and two had bilateral MI. MRI lesion topography were classified to 3 patterns: 1) The bilateral medial and the right tegmental regions in the upper and the middle medulla oblongata, 2) The right-predominant extensive regions in the lower medulla oblongata, and 3) the left lateral and tegmental regions in the lower medulla oblongata. Vascular images disclosed severe degree of atherosclerosis (atherothrombosis) in 3 patients (Fig. 2), dissection of the vertebral artery in 2 patients (Fig. 3) and dural arteriovenous fistula in one patient (Fig. 4).

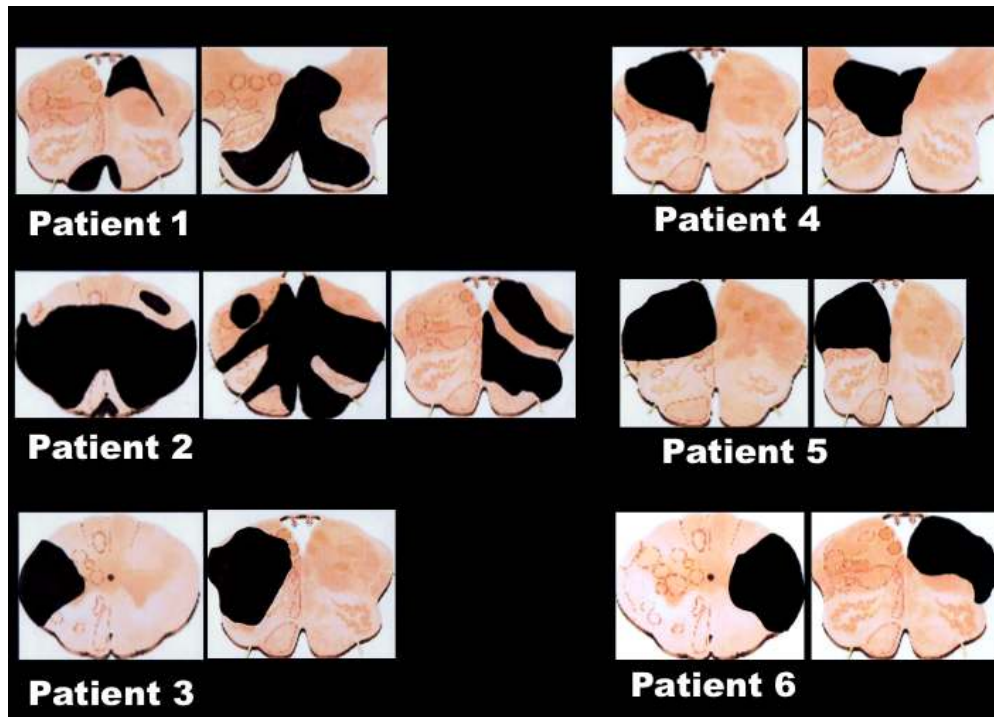


Fig. 1. Schema of lesion topography

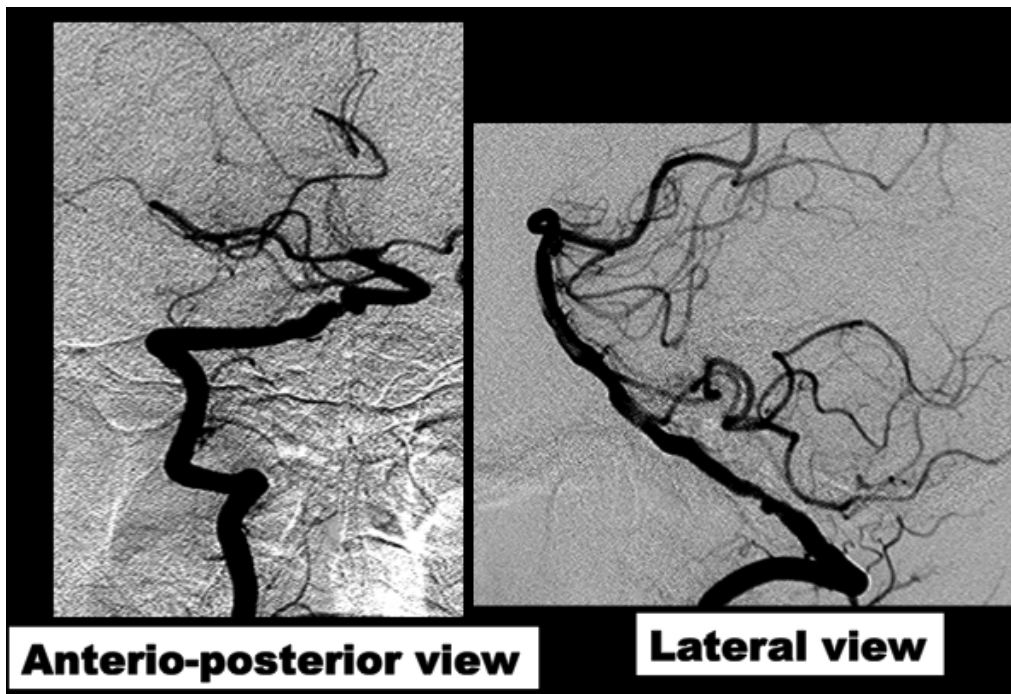


Fig. 2. Cerebral angiogram in patient 1

Severe degree of atherosclerotic changes was found in the basilar and vertebral arteries

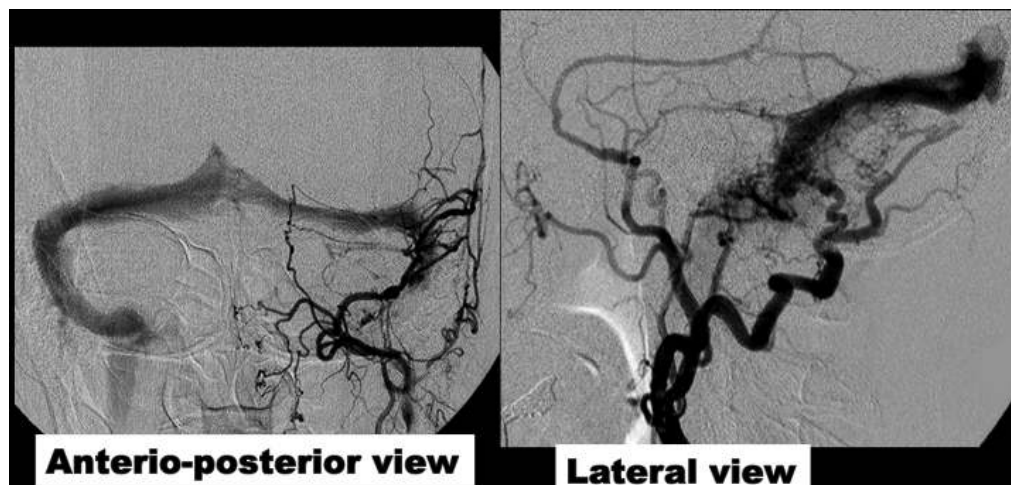


Fig. 3. MRA findings in patient 3

Marked stenosis was found in the right vertebral artery, presumably suggesting dissection in the vertebral artery

4. DISCUSSION

The present study reported that the prevalence of dyspnic MI was 0.3% in patients with acute ischemic stroke and 6.3% in MI patients. Initial neurological examination showed soft palatal palsy and absent pharyngeal reflex. The neurological profile suggested that cough syncope, hiccup, circulatory failure, bulbar palsy, sensory deficits or dysuria in dyspneic MI

patients. The frequency of hypertension was high (83%) on CVD risk factors. Radiological topography of MI disclosed the unilateral side in 4 patients and the bilateral sides in 2 patients. The arterial lesion of dyspnic MI showed atherothrombosis in 3 patients, arterial dissection in 2 patients and dural arteriovenous fistula in one patient. The prognosis was fatal or poor in 4 patients (67%).

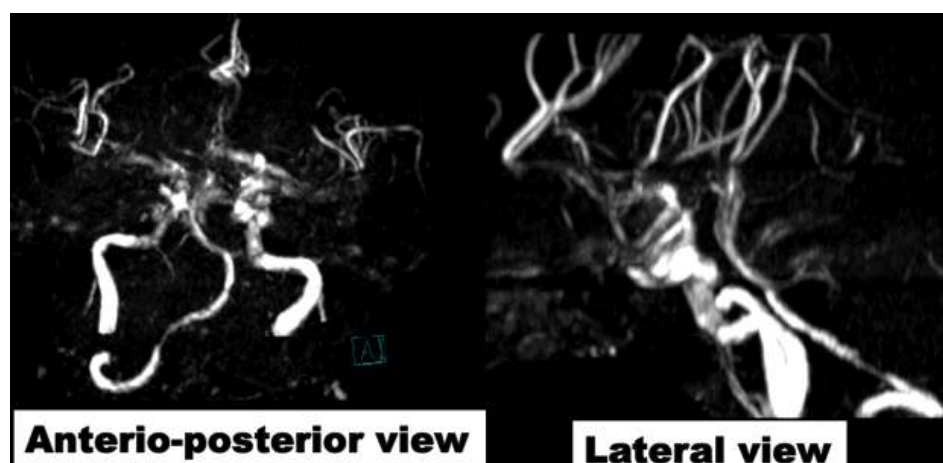


Fig. 4. Cerebral angiogram in patient 2
Dural arteriovenous fistula was found in the infratentorial region

Table 1. Clinical profile of MI patients with respiratory dysfunction

Patient	Age	Sex	Arterial lesion	Respiratory patterns	Degree of palatal palsy	Other neurological findings	Prognosis
1	78 years	Female	AT	Apnea	Mild	Hiccup, cough syncope, arrhythmia, circulatory failure	Death (recurrent MI)
2	78 years	Female	AVF	Dyspnea	Mild	Sensory deficits below the necks,	good**
3	38 years	Male	AD	Hyperventilation	Severe	Wallenberg's syndrome, BP instability	Death (recurrent MI)
4	52 years	Male	AD	Hyperventilation	Mild	Wallenberg's syndrome	Good
5	88 years	Female	AT	Hyperventilation	Moderate	Wallenberg's syndrome	Poor
6	86 years	Female	AT	Hyperventilation	Severe	Wallenberg's syndrome	Poor

*Abbreviations: AD, arterial dissection; AT, atherothrombosis; AVF, arteriovenous fistula; BP, blood pressure; MI, Medullary infarction. Patient 1 was reported previously in reference 30. * All patients had absent pharyngeal reflex. ** Intervention treatment*

Kumral et al. [8]. Described 6 patients with acute respiratory failure due to involvement of the unilateral dorsolateral medulla oblongata among 4500 consecutive inpatients with the first ischemic stroke during 7 years. The prevalence of dyspnic MI was calculated at 0.13% in patients with the first ischemic stroke [8]. The present study indicated that that was 0.3% in patients with acute ischemic stroke and 6.3% in MI patients.

Respiratory dysfunction due to the damage in the medulla oblongata was described in various diseases, including stroke, poliomyelitis, neoplasm, multiple sclerosis, syringobulbia, trauma and other causes [9-11]. The anatomical

location of the central ventilatory system has been speculated in the human. Multiple independent respiratory centers in the brainstem act upon breathing. The respiratory centers are divided into medullary and pontine centers. The medullary centers comprise 2 groups of cells: 1) A dorsal group in the nucleus of the solitary tract driving the respiratory system in the contralateral spinal cord and 2) The ventral respiratory group in the nucleus retroambiguus situated in the reticular formation around the nucleus ambiguus driving inspiratory and expiratory neurons by the vagus nerve. The pre-Bötzinger region of the ventral respiratory group has been hypothesized to be the source of intrinsic pacemaker activity that drives respiration. These dorsal and ventral

groups regulate the respiratory rhythm. The pontine center is the pneumotaxic center situated in the medial parabrachial and Kölliker-Fuse nuclei. The pontine center regulates the 2 medullary centers. Besides its rostro-caudal organization, respiration depends on a parallel system supporting voluntary, automatic and limbic control of breathing [12-14]. All 3 groups of neurons are paired bilaterally. Originally, it was thought that bilateral damage was necessary to induce central hypoventilation because each side seemed to have the ability to independently drive diaphragmatic activity. However, autopsy-proved unilateral infarction in the lateral medullary tegmentum demonstrated unequivocally that unilateral damage can cause the syndrome [15]. In such a case, damage to crossing fibers connecting the paired medullary nuclei has been proposed as a possible explanation [16]. Respiratory impairment may occur due to involvement of the efferent pathways from the medullary respiratory centers crossing to the opposite side of the medulla before descending into the spinal cord [17]. Main previous patients of dyspnic MI are listed in Table 2. Respiratory dysfunction was usually reported in patients with the unilateral MI, so called Wallenberg's syndrome [8,9,15,18-28]. Such detailed clinicopathological studies addressed that caudal brainstem stroke involving the dorsal motor nucleus of the ninth and the tenth cranial nerve, the tractus solitarius and the medullary reticular formation could trigger central respiratory failure [4,5,8,9,18-28]. The unilateral lesion topography exhibited the lateral or dorsolateral portion, including the tegmentum. The lesion side was

the left or right without significant laterality or predominance. The pathogenesis of dyspnic MI has revealed atherothrombosis, dissection or microembolism in the vertebral artery. The present study showed additional cause of dural arteriovenous fistula in one patient. The patient age might depend on the causative lesion of the vertebral artery. In patients with atherosclerotic changes or microembolism, the onset age was older than 60-70 years. Otherwise, that was younger at 30-60 years in patients with the vertebral artery dissection compared to atherothrombotic patients.

Respiratory dysfunction generated from a few hours to several days after MI onset. The most of patients had dyspnea within 5 days of acute phase [8,9,15,18-21,23-25]. However, the delayed development of central apnea at more than 9 days after MI was also described in several cases [22,26-28]. The delayed mechanism of respiratory dysfunction from 7 days to 3 months post-infarction could contribute to thrombus spreading, peri-infarctive edema, secondary neuronal degeneration, apoptosis, or abnormal plasticity involving local synaptic interconnections after MI. Neurological examination suggested dysphagia or hiccup frequently in previous patients with dyspnic MI, besides the distinct tomography of sensory deficits, Horner's sign and ataxia of Wallenberg's syndrome [8,9,15-28]. The present study disclosed that all patients had absent pharyngeal reflex and variable degree of soft palatal palsy. The nucleus ambiguus, the glossopharyngeal and the vagus nerve might be damaged in our

Table 2. Main previous cases of MI patients with respiratory dysfunction

Authors (reported year)*	Patient number	Lesion side
Askenasy (1988) [9]	1 patient	Left
Hashimoto (1989) [18]	1 patient	Left
Bogousslavsky (1990) [19]	2 patients	Left (1), right (1)
Takehara (1992) [20]	1 patient	Right
Levin (1997) [15]	1 patient	Left
Iwasaki (2001) [21]	1 patient	Right
Oya (2001) [22]	1 patient	Right
Terao (2004) [23]	1 patient	Left
Takabatake (2005) [24]	1 patient	Left
Lassman (2005) [25]	1 patient	Right
Arai (2008) [26]	2 patients	Right (2)
Kumral (2011) [8]	6 patients	Left (4), right (2)
Mendoza (2013) [27]	1 patient	Left
Sugawara (2014) [28]	1 patient	Right
Present study	6 patients	Left (3), right (1), ilateral (2)

*Reference number, Abbreviations: MI, Medullary infarction

patients. The medullary respiratory center was located around the nucleus ambiguus driving inspiratory and expiratory neurons by the vagus nerve [12-14]. Therefore, pharyngeal reflex and paralysis might be crucial and predictive findings for developing respiratory dysfunction in MI patients.

CVD risk analyses of our patients with dyspnic MI revealed hypertension in 5 patients, smoking in 2 patients and arrhythmia in one patient. A previous clinicoradiological study of sleep-related breathing disorders (SRDB) was reported in 68 patients with acute first-ever lacunar stroke. The apnea/hypopnea index (AHI) was determined using respiratory polygraphy. Smoking and body mass index (BMI) were associated with AHI \geq 30 in the multivariate analysis. SRDB screening was noted in smokers with capsular or pontine lacunar stroke [29]. In the present study, the prognosis was fatal in 2 patients even if mechanical ventilator was used. Previously 2 patients died at 1-11 months after MI onset [8,25]. Two of our patients (25%) died from recurrent ischemic stroke. On CVD risk factors of our fatal patients, two had hypertension and non-smoking. BMI was 19.2 kg/m² in Patient 1 and 24.0 in Patient 3. Both patients had no prior history of sleep apnea. Patient 1 had 2nd MI at 3 months later. Patient 3 developed recurrent MI at two days after the first MI. In particular, the prognosis was fatal in those patients who accompanied circulatory changes of blood pressure and heart rate. Tonic and reflex activity of medullary neurons that mediate sympathetic and parasympathetic cardiovascular reflexes is affected by respiration, and these vasomotor centers are located in close proximity to the ventral respiratory group and dorsal respiratory group. Instability of blood pressure and heart rate has been reported after lateral medullary infarction in association with central hypoventilation. The respiratory center seems to exist near the circulatory center and the urinary center in the medulla oblongata. In general, the mortality of dyspnic MI was higher in patients with the atherothrombosis compared to microembolism and arterial dissection [8,25,30]. The present and previous patients supported that high frequency of bulbar palsy in patients with dyspnic MI. Circulatory instability of blood pressure and heart rate might be a fatal neurological indicator.

5. CONCLUSION

The present study indicated that the prevalence of dyspnic MI was 0.3% in patients with acute

ischemic stroke and 6.3% in MI patients. Neurological examination revealed cough syncope, hiccup, circulatory instability, bulbar palsy, sensory deficits or dysuria. Particularly, pharyngeal areflexia and soft palatal palsy was found on initial examination. These pharyngeal findings might be alerted to development of dyspnea in MI patients. The frequency of hypertension was highest on CVD risk factors. The prognosis was fatal in 2 patients (33%). Radiological topography disclosed unilateral MI in 4 patients and bilateral MI in 2 patients. The pathogenesis of dyspnic MI could contribute to atherothrombosis, arterial dissection and dural arteriovenous fistula. Infarctive side and size were not correlated with the prognosis. The atherothrombotic lesion and circulatory failure could contribute to poor recovery or high mortality in patients with dyspnic MI.

CONTENT

All authors declare that written informed consent was obtained from all patients for publication of this study and accompanying images.

ETHICAL APPROVAL

The authors have obtained ethical approval from the ethical committee of Toho University Omori Medical Center.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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