



Case Report

Cerebral embolization associated with parenchymal seeding of the left atrial myxoma: Potential role of interleukin-6 and matrix metalloproteinases

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Systemic embolization has been reported in up to 40% of patients with left atrial myxoma, half of them with cerebral involvement. However, development of intracerebral embolization associated with parenchymal seeding of the myxoma emboli is an extremely rare complication, with only 36 histologically diagnosed cases reported in the published literature. We describe a 69-year-old woman who arrived at the emergency service with hemiparesis associated with drug-resistant epilepsy and a medical history of resection of a left atrial myxoma 10 months previously. Cranial computed tomography revealed multiple large lesions of heterogeneous density and cystic components in the occipital lobes and posterior fossa parenchyma. Histopathological analyses after stereotactic biopsy of the occipital lesion revealed infiltrative myxoma cells with benign histological findings and uniform expression of calretinin similar to that of the primary cardiac myxoma. Additional immunohistochemical studies confirmed brain parenchymal seeding of the myxoma cells with strong expression of interleukin-6 (IL-6) and focal expression of matrix metalloproteinases-2 (MMP-2). Here, we discuss the clinicopathological features of intracerebral embolization of left atrial myxomas associated with progressive parenchymal seeding of the tumor emboli and the potential pathogenic role of IL-6 and MMPs.

Key words: left atrial myxoma, embolus, interleukin-6, MMP-2, MMP-9.

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INTRODUCTION

Cardiac myxoma is the most frequent primary cardiac tumor and comprises approximately 70% of primary neoplasms in the heart.¹ Clinically, cardiac myxoma has a wide presentation, ranging from constitutional symptoms to occlusive or embolic events.² Within this broad clinical spectrum, embolic events represent the hazardous manifestation of the disease, and are usually caused by tumor fragments or even complete detachment of the tumor.^{3–6}

Systemic embolization occurs in approximately 30–40% of patients with cardiac myxoma.^{7,8} As 75–80% of the tumors arise in the left atrium, approximately half of the embolic events may affect the central nervous system (CNS).⁹ The neurological manifestation of cerebral embolization depends on whether embolic tumor cells remain intraluminal, leading to ischemic stroke, invade the vessel wall, resulting in intracranial aneurysms, or, in rare circumstances, transgress the vessel wall, leading to brain parenchymal seeding.¹⁰

Factors related to the intracranial dissemination of left cardiac myxomas remain unidentified.¹¹ Some studies suggest a positive correlation between interleukin-6 (IL-6), matrix metalloproteinase (MMP)-2, and MMP-9, and increased risk of embolic events and intracranial aneurysms in left cardiac myxoma patients.^{12–14} However, the role of MMPs and IL-6 in the parenchymal seeding of the tumor emboli remains unknown.

In this article, we describe a case of cerebral and cerebellar embolization with parenchymal seeding and high expression of IL-6 and MMP-2 after surgical resection of a left atrial myxoma. Moreover, we summarize a detailed review of the literature on intracranial embolization associated with parenchymal seeding, focusing on the potential pathogenic role of IL-6 and MMPs.

CLINICAL SUMMARY

A 69-year-old woman with a medical history of drug-resistant epilepsy for the past four months was admitted to the emergency service with acute left-side hemiparesis and distal tremor in both the hands. Ten months prior, she had undergone total excision of a sporadic left atrial myxoma at another institution. A deeper analysis of her medical history revealed repeated recurrent ischemic strokes several months before the heart surgery. No cardiac lesion was detected by echocardiography. Biochemical tests revealed high levels of C-reactive protein (4.3 mg/dL) and lactate dehydrogenase (538 U/L) in blood. Other tests, such as complete blood counts and metabolic panel, were normal.

Cranial computed tomography (CT) revealed cortical and subcortical hyperdense nodules surrounded by the vasogenic edema zone in the posterior fossa and cerebral hemispheres. Those lesions were predominantly located in the frontal, occipital, and cerebellar regions and were initially suspected as hemorrhagic events (Fig. 1). No magnetic resonance imaging (MRI) studies were performed due to unavailability of equipment. A stereotactic biopsy of the right occipital lesion was performed. The patient, with large and multiple intracranial lesions, died 30 months after initial cardiac surgery.

PATHOLOGICAL FINDINGS

The histologic findings showed brain parenchyma with hemorrhagic areas surrounded by abundant mucoid matrix containing sparse spindle-shaped or stellate cells. Tumor cells had oval nuclei and eosinophilic cytoplasm without nuclear pleomorphism or mitosis (Fig. 2). Immunohistochemical analyses confirmed parenchymal seeding of the myxoma cells with strong expression of calretinin (Fig. 3A). Multiple old hemorrhagic foci with clusters of hemosiderophages were also found. Based on these findings, we conclude a diagnosis of intracerebral embolization

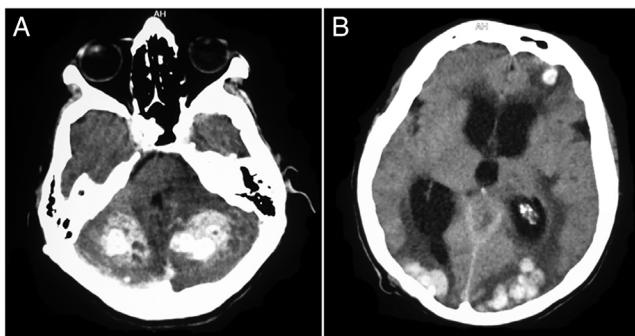


Fig. 1 CT findings of the brain. Axial images display multiple hyperdense nodules in cortical and subcortical regions of the cerebellum (A) and the frontal and occipital (B) lobes as well as subsequent hydrocephalus.

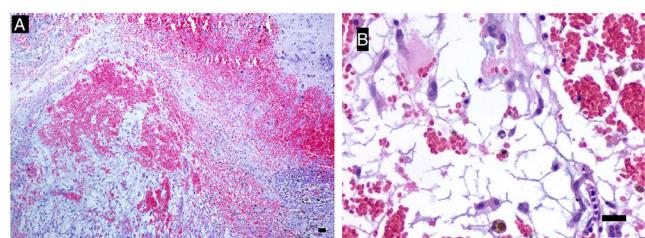


Fig. 2 Histological findings on the metastatic brain tumor biopsy specimen sections stained with HE. (A) The tumor shows abundant lepidic cells in a myxoid stroma infiltrating brain parenchyma in a bleeding background. (B) The tumor cells exhibit nuclear pleomorphism and mitotic figures (B). Scale bars: 100 μ m (A), 50 μ m (B).

of left atrial myxoma associated with large solid intraparenchymal lesions. Moreover, aiming to assess the role of the IL-6 and MMPs, we found high expressions of IL-6 (Fig. 3B), focal expression of MMP-2 (Fig. 3C), and negative expression of MMP-9 (Fig. 3D) in the tumor cells. Double immunohistochemical staining was initially planned. However, the lack of experience in our country prevented performing this procedure.

Review of original tissue sections of the surgically treated primary cardiac tumor revealed a left atrial myxoma with a papillary pattern, benign histological features, and uniform expression of calretinin into the myxoma cells (Fig. 4).¹⁵

DISCUSSION

We describe a patient with intracerebral embolization of left atrial myxoma associated with large parenchymal lesions. Here, we have confirmed that IL-6 and MMP-2 were expressed in intracranial embolic myxoma cells.

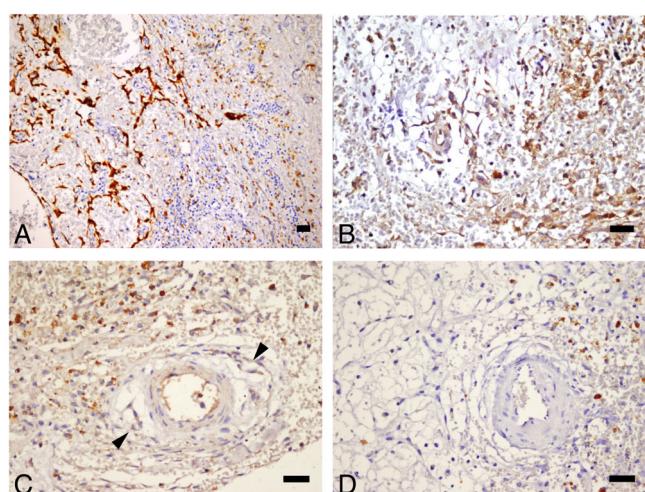


Fig. 3 Immunohistochemical observations on the metastatic brain tumor biopsy specimen sections stained for calretinin (A), IL-6 (B), MMP-2 (C), and MMP-9 (D). The tumor cells are immunoreactive for calretinin (A), IL-6 (B), and MMP-2 (C). MMP-9 immunoreactivity is detected only in inflammatory cells (D) but undetectable in the tumor cells (D). Scale bars: 50 μ m (A-D).

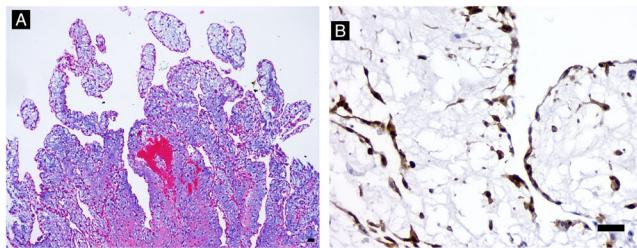


Fig. 4 Histological (A) and immunohistochemical (B) observations on the metastatic brain tumor biopsy specimen sections stained with HE (A) and immunostained for calretinin (B). At a low magnification, villous-type myxoma with numerous friable fronds is observed (A). At a higher magnification, myxoma cells are immunoreactive for calretinin (B). Scale bars: 250 µm (A), 50 µm (B). Scale bars: 250 µm (A), 50 µm (B).

Cardiac myxomas are benign tumors usually located in the left atrium and can embolize to several extracardiac tissues. Two gross subtypes of cardiac myxomas have been described: the solid type and the villous type. The villous-type tumors have an irregular, often friable, and papillary surface, as observed in our case. Immunohistochemical studies revealed uniform expression of calretinin in nearly all cardiac myxoma cases.¹⁵ The brain is the most frequent embolization site.¹ Neuroimaging studies have demonstrated that ischemic infarction events are the most frequent neurological findings (76.0–88.8%) in patients harboring left atrial myxomas with neurological manifestations.^{6,16} In contrast, the exact prevalence of late neurological complications in these patients is unknown because long-term studies evaluating the likelihood of delayed neurological complications have not been conducted. The largest single-center study, by Brinjikji *et al.*, in 47 patients treated for left atrial myxoma, reported that intracranial aneurysm and extravascular “metastasis” represented infrequent neuroimaging findings during the follow up of these patients (observed in 14.9% and 4.3% of cases, respectively).¹⁷ However, Zhang *et al.* followed 12 patients treated for left atrial myxoma with predominant neurological manifestations. They found that eight (67%) patients had multiple intracranial aneurysm, and that six (50%) patients exhibited extravascular “metastasis”.¹⁸

Although the mechanisms of embolization of a benign tumor and metastasis of an invasive malignancy are fundamentally different, the appearance of multiple lesions at a distant site in the setting of a cardiac myxoma has occasionally been referred to (erroneously) in the literature as “metastasis.”^{17,18} Since the first description made by Rankin *et al.*, in 1978,¹⁹ our comprehensive review revealed 36 histologically established cases of intracerebral embolization associated with parenchymal brain invasion from a benign left atrial myxoma (Table 1).^{10,14,18–51} A careful review of the cases confirmed that three patients have been reported twice,^{14,19,20,23,24,28} six patients had

unavailable histological proof,^{37,52–56} and four apparent primary cardiac sarcomas were erroneously reported as a cardiac myxoma.^{57–60} In one case, the original report could not be located,⁶¹ and another report described embolic myxoma cells in the leptomeninges without evidence of parenchymal seeding.⁶²

A summary of our review shows that cerebral embolization associated with parenchymal lesions usually occurs in adults of mean age of 47.6 ± 14.6 (range 15–70) years. There is a clear female predominance (male:female = 1:2). This rare condition might occur many years before, simultaneously with, or many years after the surgical excision of the primary tumor. Most patients (74.3%) developed intracerebral embolization several months after resection of the cardiac tumor (from 4 to 144 months), and in around 77.8%, multiple brain regions were involved. Left atrial myxomas preferentially lodge in the middle cerebral artery system.⁶³ Thus, parietal and occipital lobes are the most affected regions (91.6%). Moreover, the bone^{19,35,46} and the skin^{23,50} can be simultaneously involved. The most common clinical presentation of these patients was seizures (37.1%), followed by headache (31.4%), and hemiparesis (20%). However, unusual presentations such as gait disorders^{37,42,50} and visual disturbances^{25,27,43} have also been reported. In addition, the high frequency of intracranial aneurysms (75%) in these patients suggests that invasion and proliferation of myxoma cells into the vessel wall might represent a previous step to brain parenchymal seeding.

Although cerebral involvement occurred in almost half of patients with embolic events, it is currently suspected that only a small portion of distant embolic myxoma may progress to parenchymal seeding of tumor cells. No risk factors for the development of this rare complication are known, but previous history of multiple recurrent neurological symptoms associated with left atrial myxoma, such as multiple ischemic strokes or recurrent seizures, may increase the risk of their appearance. Indeed, up to 70.8% of patients with late-onset cerebral embolization associated with parenchymal seeding of the tumor cells presented with prominent neurologic symptoms during initial admission. This finding suggests that left atrial myxomas with previous history of multiple recurrent strokes are more likely to develop delayed neurological manifestations during follow up.^{10,17}

Despite multiple parenchymal seeding, the histology of the primary and embolic tumor infiltrates remains benign without evidence for malignant transformation. Histological evaluation of primary tumor frequently reveals benign cardiac myxomas with prominent papillary surface projections.^{19,24,29,49} Occasionally, cardiac myxofibrosarcomas⁶⁴ or metastatic adenocarcinomas^{10,30} might resemble cardiac myxomas. Based on these circumstances, calretinin

Table 1 Cerebral embolization associated with parenchymal seeding of the left atrial myxoma reported in the literature

Year	Author	Age/ sex	Interval between myxoma surgery and embolization	Initial symptom of the disease	Clinical presentation of the embolism	Location	Aneurysm formation	Other embolisms	Treatment	Outcome	Survival
1978	Rankin LI, Seo IS Budzilovich G	44 F	+96 months	Recurrent stroke NAD	Hemiparesis, aphasia Death on arrival	Choroid plexus P, cerebellum, dura	NAD	Bone	Surgery	Alive	72 months
1979	Bazin A	52 F	Post-mortem	NAD	NAD	Cerebrum- cerebellum F-P	NAD	—	No	Death	NAD
1987	Morimoto K, Kadota T Ng HK	56 F	+48 months	Recurrent stroke NAD	Hemiparesis, seizures Visual disturbances, seizures	NAD	—	Surgery	NAD	NAD	NAD
1990	Chozick BS Chen HJ	44 M	+11 months	Unspecific Hematuria	Seizures Headache, visual disturbances Hemiparesis	O	NAD	—	Surgery	Alive	24 months
1992	Wada A, Kanda T Samaratunga H	61 F 68 F	+8 months +12 months	Recurrent stroke Seizures	Seizures P, dura	NAD	—	Surgery	Alive	84 months	24 months
1993	Scarpelli M	70 M	-9 months	NAD	Unspecific symptoms Hemiparesis	P-O	NAD	—	Surgery	Alive	1 month
1994	Hirudayaraj P	64 M	-7 months	Hemiparesis	Seizures Hemiparesis	P	NAD	—	Surgery	Alive	14 months
1997	Altundang MB	50 F	+144 months	Dyspnea	Seizures Hemiparesis, seizures	F-P-O, cerebellum F-O	NAD	—	Surgery	NAD	NAD
2004	Balasuriya BM	41 F	+15 months	Seizures	Hemiparesis, seizures	Yes	NAD	—	Surgery	Alive	24 months
2005	Rodrigues D	65 M	+48 months	NAD	Hemiparesis, Seizures	P-O	NAD	—	Surgery + RT	NAD	NAD
2010	Rodriguez F	41 F	+12 months	paresthesia / visual disturbance	Seizures, paresthesia	F-P-O	Yes	Bone	Surgery	Alive	63 months
2006	Moiyadi AV Rabarijaona M	35 M 53 F	-22 months +48 months	Seizures Seizures	Seizures Seizures	F-P-T-O F-P-O, cerebellum P-O, cerebellum Multiple	NAD Yes	—	RT Surgery	Alive Alive	6 months NAD
2007	Wolf M	60 M	+9 months	Palpitations	Seizures, hemiparesis Headache	No	—	—	Conservative	Alive	78 months
2008	Suzuki R	68 M	+6 months	Stroke	—	NAD	—	Surgery + RT	Alive	NAD	NAD
2008	Eddleman C Kumar A Badriyah	18 M 30 F 15 F	+4 months +24 months +44 months	Dyspnea Seizures NAD	Headache Seizures Headache	O F-P-O P-O	Yes Yes NAD	—	Surgery Conservative Surgery	Alive Alive Alive	NAD NAD 12 months

(Continues)

Table 1 (Continued)

Year	Author	Age/ sex	Interval between myxoma surgery and embolization	Initial symptom of the disease	Clinical presentation of the embolism	Location	Aneurysm formation	Other embolisms	Treatment	Outcome	Survival
2012	Radoi MP	45 M	+18 months	NAD	Seizures, hemiparesis	F-P	Yes	—	Surgery	Alive	12 months
2013	Rique J	42 F	Simultaneous	amaurosis	Amaurosis	F-O	NAD	—	Surgery	NAD	NAD
2015	Côté I	46 F	+24 months	Seizures	Seizure	F-P	No	—	Surgery	Alive	12 months
2016	Castañón- Leon A	40 F	-1 month	Dyspnea	Headache	F-P-O, cerebellum	Yes	—	Surgery + RT	Alive	NAD
2017	El Sabbagh	41 F	-24 months	Headache, hemiparesis	Headache, hemiparesis	F	NAD	Bone	Surgery	NAD	NAD
2017	Ryu J	43 F	+9 months	Stroke	Seizure	P	NAD	—	Surgery + RT	NAD	NAD
2019	Wan Y	39 F	+7 months	NAD	Headache, visual disturbances	F-P-O	Yes	—	Surgery	Alive	11 months
2019	Roque A	48 F	-5 months	Headache	Headaches	F-P-O	Yes	—	RT	Alive	18 months
2019	Zhang S	49 F	+11 months	NAD	Headaches	P-O	Yes	—	NAD	Alive	23 months
2019		16 F	+34 months	NAD	Hemiparesis	P-O	Yes	—	NAD	Alive	113 months
2019		39 F	+8 months	NAD	Hemiparesis	P-O	Yes	—	NAD	Alive	32 months
2019		39 F	+8 months	NAD	Headaches	P-O	No	—	NAD	Alive	21 months
2020	Maas JA	62 M	-3 months	Hemiparesis	Hemiparesis, blurred vision	F-P-O	NAD	Skin	Surgery	Alive	48 months
2020	Panos	63 M	+9 months	Stroke	Seizures	P-O	Yes	—	RT	Alive	36 months
2020	Present case	69 F	+10 months	Recurrent stroke	Seizures, distal tremor	F-P-O, cerebellum	NAD	—	Conservative	Death	30 months

immunohistochemistry is paramount for the proper identification of embolic cardiac myxomas. In our review, only seven of 36 cases evaluated calretinin expression in the infiltrative tumor cells.^{35,39,43,45,47,49}

Although the mechanism of the brain parenchymal seeding after complete local resection of cardiac myxomas has not been elucidated, embolic tumor cells might remain active and invade the wall of the distant vessels.^{29,35,39,45} Traditionally, the vasa vasorum has been considered a key element for the embolization of tumor particles. Thus, small particles entering in the vasa vasorum penetrate the subintimal tissue, leading to subsequent fragmentation of the arterial wall.^{42,45} However, this explanation seems incomplete because the existence of vasa vasorum has only been demonstrated in proximal intracerebral arteries,^{65,66} and most cerebral emboli occur predominately in distal intracerebral arteries.^{6,42,45,67} In contrast, some authors suggest that the viable tumor particles may cause progressive disruption of the internal elastic lamina through a direct transendothelial invasion rather than hematogenous seeding via vasa vasorum.^{21,45} Several histological studies have demonstrated that proliferation of myxoma cells in the arterial wall^{29,35,39,45} behave like a nidus for aneurysm formation and an anchor for subsequent growth of the extravascular tumor tissue.

The mechanisms by which cardiac myxoma cells penetrate the cerebral vessel wall remain unknown. Some authors have proposed that IL-6 produced by cardiac myxoma may play a crucial role in the adhesiveness of myxoma cells to cerebral vascular endothelial cells, through the induction of intercellular adhesion molecule-1 (ICAM-1) during intracerebral embolization.¹⁴ In addition, Yaguchi *et al.*⁶⁸ reported an isolated increase in IL-6 levels in cerebrospinal fluid (CSF), in contrast to normal serum levels, in a patient with multiple newly formed intracranial aneurysms after resection of a cardiac myxoma. These findings suggest that the high level of IL-6 in CSF reflects overproduction of IL-6 by embolic myxoma cells in the intracranial vessel. In light of these previous hypotheses,^{14,67-69} we are reporting for the first time the direct evidence for IL-6 expression in embolic tumor cells of a left atrial myxoma within brain parenchyma.

Increased systemic and local production of IL-6 has been reported in patients with cerebral aneurysms associated with cardiac myxomas.^{14,67-69} IL-6 stimulates the gene expression of some MMPs, including MMP-2 and MMP-9, via the activator protein-1 pathway.⁷⁰ MMP-9 is known to break the blood-brain barrier and probably to facilitate the CNS invasion of myxoma cells.⁷¹ Cultured cells of the embolic myxomas treated with IL-6 had a higher increase in the activity of both MMP-2 and MMP-9 than cells from non-embolic myxomas.⁷² The proteolytic role of MMPs in expansion of trophoblasts

and cancer cells is well described.^{73,74} Among the MMP superfamily, MMP-2 and MMP-9 are essential for the fragmentation of the internal elastic lamina in both clinical and experimental model studies.⁷⁵⁻⁷⁷ In the present case, we could demonstrate the expression of MMP-2 in infiltrative myxoma cells. This finding might suggest that MMP-2 play a more sustainable role in brain parenchymal seeding of myxoma cells than MMP-9.^{78,79}

Since the first resection of a cardiac myxoma in 1953, the standard treatment of these tumors has been surgical removal to reduce the rate of embolic events.⁸⁰ In contrast, the standard management of intracerebral embolization after resection of the primary cardiac tumor has not been well established due to its rarity and variable clinical course. In our review, similar to the primary cardiac tumor, surgery was the most frequent therapeutic option in patients with accessible brain lesions. Radiotherapy has been frequently conducted for patients with multiple or progressive lesions, with promising results, although clinical follow up managements are limited.^{10,32,38,45,47,49,51} Considering that these lesions have persistently active tumor cells, adjuvant chemotherapy would be a reliable option to reduce the risk of extracardiac seeding. However, no previous information on experiences in the management of this therapeutic option in cardiac myxomas is available. Currently, surgical resection associated with radiotherapy is widely used to stabilize the progressive neurological complications in these patients.^{32,38,45,47}

Further research is still required to understand the behavior of left atrial myxoma. However, careful attention should be paid to the neurological symptoms of the patients to detect delayed neurological complications. With complete surgical resection of the cardiac myxoma, strict follow up of the patients should still occur.

Although the left atrial myxoma is a benign tumor, it has the potential to embolize, especially in the brain. Cerebral embolization associated with progressive parenchymal seeding of the tumor is an extremely rare complication that may occur several years after surgical removal of the primary cardiac tumor. The appearance of recurrent neurological symptoms during the clinical course of left atrial myxoma may be a risk factor for late-onset neurological manifestations. Our case supports previous observations that the expression of IL-6 and MMP-2 in myxoma cells favors progression of the intracranial embolic process. Thus, future research is essential to determine the diagnostic and therapeutic application of these markers for the tumor.

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DISCLOSURE

The authors have no personal financial or institutional interest in any of the drugs, materials, and devices described in this article.

REFERENCES

1. Basso C, Valente M, Poletti A, Casarotto D, Thiene G. Surgical pathology of primary cardiac and pericardial tumors. *Eur J Cardiothorac Surg* 1997; **12**: 730–737.
2. Bartoloni G, Pucci A. Cardiac myxoma. In: Basso C, Valente M, Thiene G (eds), *Cardiac Tumor Pathology*. Totowa, NJ: Humana Press, 2013; 31–44.
3. Desousa A, Muller J, Campbell RL, Batnitzky S, Rankin L. Atrial myxoma: A review of the neurological complications, metastases, and recurrences. *J Neurol Neurosurg Psychiatry* 1978; **41**: 1119–1124.
4. Alvarez-Sabin J, Lozano M, Sastre-Garriga J et al. Transient ischaemic attack: A common initial manifestation of cardiac myxomas. *Eur Neurol* 2001; **45**: 165–170.
5. Ekinci EI, Donnan GA. Neurological manifestations of cardiac myxoma: A review of the literature and report of cases. *Intern Med J* 2004; **34**: 243–249.
6. Lee VH, Connolly HM, Brown RD Jr. Central nervous system manifestations of cardiac Myxoma. *Arch Neurol* 2007; **64**: 1115–1120.
7. Boyacioglu K, Kalender M DA et al. Outcomes following embolization in patients with cardiac myxoma. *J Card Surg* 2017; **32**(10), 621–626.
8. Pinede L, Duhaut P, Loire R. Clinical presentation of left atrial cardiac Myxoma A series of 112 consecutive cases. *Medicine (Baltimore)* 2001; **80**: 159–172.
9. Boyacioglu K, Ak A, Dönmez AA, Çayhan B, Aksüt M, Tuncer MA. Outcomes after surgical resection of primary non-Myxoma cardiac tumors. *Braz J Cardiovasc Surg* 2018; **33**: 162–169.
10. Moiyadi AV, Moiyadi AA, Sampath S et al. Intracranial metastasis from a glandular variant of atrial myxoma. *Acta Neurochir* 2007; **149**: 1157–1162.
11. Parissis JT, Mentzikof D, Georgopoulou M, Gikopoulos M, Merkouris K, Kefalas C. Correlation of interleukin-6 gene expression to immunologic features in patients with cardiac myxomas. *J Interferon Cytokine Res* 1996; **593**: 589–593.
12. Koo Y, Kim T, Kim O. Neurosurgical SO-J of K, 2009 U. multiple fusiform cerebral aneurysms and highly elevated serum interleukin-6 in cardiac myxoma. *J Korean Neurosurg Soc* 2009; **45**: 394–396.
13. Ezerioha N. Intracardiac myxoma, cerebral aneurysms and elevated interleukin-6. *Case Rep Neurol* 2015; **29425**: 152–155.
14. Wada A, Kanda T, Hayashi R, Imai S, Suzuki T, Murata K. Cardiac myxoma metastasized to the brain: Potential role of endogenous Interleukin-6. *Cardiology* 1993; **83**: 208–211.
15. Terracciano LM, Mhawech P, Suess K et al. Calretinin as a marker for cardiac myxoma. Diagnostic and histogenetic considerations. *Am J Clin Pathol* 2000; **114**: 754–759.
16. Stefanou M, Rath D, Stadler V et al. Cardiac Myxoma and cerebrovascular events: A retrospective cohort study. *Front Neurol* 2018; **9**: 1–10.
17. Brinjikji W, Morris J, Brown R et al. Neuroimaging findings in cardiac myxoma patients: A single-center case series of 47 patients. *Cerebrovasc Dis.* 2015; **40**: 35–44.
18. Zhang S, Zhang Q, Yu H et al. Neuroimaging characteristics and long-term prognosis of myxoma-related intracranial diseases. *Neuroradiology* 2019; **62**: 307–317.
19. Rankin LI, DeSousa AL. Metastatic atrial myxoma presenting as intracranial mass. *Chest* 1978; **74**: 451–452.
20. Seo IS, Warner TF, Colyer RA, Winkler RF. Metastasizing atrial myxoma. *Am J Surg Pathol* 1980; **4**: 391–399.
21. Budzilovich G, Aleksic S, Greco A, Fernandez J, Harris J, Finegold M. Malignant cardiac myxoma with cerebral metastases. *Surg Neurol* 1979; **11**: 461–469.
22. Bazin A, Peruzzi P, Baudrillard J, Pluot M, Rousseaux P. Cardiac myxoma with cerebral metastases. *Neurochirurgie* 1987; **33**: 487–489.
23. Morimoto K, Fujita T, Wakayama A et al. Cardiac myxoma metastatic to the brain. *No To Shinkei* 1986 (In Japanese.); **38**(9), 865–865.
24. Kadota T, Imakita S, Mitomo M et al. Metastatic brain tumor of atrial myxoma. *Neuroradiology* 1987; **29**: 218.
25. Ng HK, Poon WS. Cardiac myxoma metastasizing to the brain. *J Neurosurg* 1990; **72**: 295–298.
26. Chozick BS, Ambler MW, Stoll J. Malignant astrocytoma six years after the resection of a cerebral metastatic cardiac Myxoma. *Neurosurgery* 1992; **30**: 923–926.
27. Chen H, Liou C, Chen L. Metastatic atrial myxoma presenting as intracranial aneurysms with hemorrhage: Case report. *Surg Neurol* 1993; **40**: 61–64.
28. Kanda T, Sakamaki T, Murata K. A cardiac myxoma with interleukin-6 production and cerebral metastasis. *Int J Cardiol* 1994; **45**: 144–146.

29. Samaratunga H, Searle J, Cominos D, Fevre IL. Cerebral metastasis of an atrial myxoma mimicking an epithelioid hemangioendothelioma. *Am J Surg Pathol* 1994; **18**: 107–111.

30. Scarpelli M, Montironi R, Ricciuti R, Vecchioni S, Pauri F. Cardiac myxoma with glandular elements metastatic to the brain 12 years after the removal of the original tumor. *Clin Neuropathol* 1997; **16**: 190–194.

31. Hirudayaraj P, Arya B, Suvarna SK, Payne G, Palaniswamy A. Myxomatous meningeal tumour: A case of “metastatic” cardiac myxoma. *Int J Cardiol* 2004; **96**: 471–473.

32. Altundag MB, Ertas G, Ucer AR et al. Brain metastasis of cardiac Myxoma: Case report and review of the literature. *J Neurooncol* 2005 Nov; **75**: 181–184.

33. Balasuriya B, Wijesekara JC, Perera S. An unusual case of focal epilepsy. *Ceylon Med J* 2010; **3**: 3–4.

34. Rodrigues D, Matthews N, Scoones D, Aziz F, Nath F. Recurrent cerebral metastasis from a cardiac myxoma: Case report and review of literature. *Br J Neurosurg* 2006; **20**: 318–320.

35. Rodriguez FJ, Brown RD, Mohr JP et al. Embolic atrial myxoma with neoplastic aneurysm formation and haemorrhage: A diagnostic challenge. *Neuropathol Appl Neurobiol* 2006; **32**: 213–216.

36. Rabariaona M, Penchet G, Adnane B, Loiseau H, Rougier A. Brain metastasis of cardiac myxoma: Case report. *Revue Tropicale de Chirurgie* 2007; **1**: 54–56.

37. Wolf M, Wibail A, De Jonghe P et al. Delayed hemorrhagic cerebral metastases after atrial myxoma resection: Report of two cases and review of the literature. *Eur J Radiol* 2008; **66**: 75–79.

38. Suzuki R, Watanabe T, Hirayama R et al. Case with cardiac myxoma causing cerebral metastasis after cardiac tumor resection. *Kyobu Geka* 2008. (In Japanese.); **61**: 456–459.

39. Eddleman CS, Gottardi-Littell NR, Bendok BR, Batjer HH, Bernstein RA. Rupture of cerebral Myxomatous aneurysm months after resection of the primary cardiac tumor. *Neurocrit Care* 2010 Oct 30; **13**: 252–255.

40. Kumar A, Deopujari CE, Karmarkar VS. Case report a rare diagnosis of multiple hemorrhagic metastases in brain. *J Postgrad Med* 2011; **57**: 214–218.

41. Idris B, Razman S, Harun R, Naik VR, Tan YC. Brain metastasis of atrial myxoma: Case report. *Med J Malaysia* 2012; **67**: 613–615.

42. Radoi MP, Stefanescu F, Arsene D. Brain metastases and multiple cerebral aneurysms from cardiac myxoma: Case report and review of the literature. *Br J Neurosurg* 2012; **26**: 893–895.

43. Riqué J, Poveda P, Sánchez R, Calvo M, Ortega J. Metástasis Cerebral de Mixoma Cardíaco Reporte de un Caso y Revisión Literaria. *Rev Argent Neuropatol* 2013; **27**: 140–142.

44. Côté Ian, Sinclair John, Woulfe John, Glikstein Rafael, Veinot John. Cerebral Metastasis Presenting after Complete Primary Resection of Atrial Myxoma: Case Report. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*. 2015; **42**: 6:457–460. <http://dx.doi.org/10.1017/cjn.2015.293>.

45. Castaño-Leon AM, Hernandez-Lain A, Maroñas L et al. Pathology-confirmed cerebral arterial invasion and recurrent multiple brain metastasis from cardiac myxoma without evidence of disease after surgery and radiotherapy. *Clin Neuropathol* 2016; **35**: 84–88.

46. El Sabbagh A, Al-Hijji MA, Thaden JJ et al. Cardiac myxoma: The great mimicker. *JACC Cardiovasc Imaging* 2017; **10**: 203–206.

47. Ryu J, Kwon J, Lee D, Yang D, Kim W. Cerebral metastatic myxoma in a cerebral infarction patient after complete resection of cardiac myxoma. *J Korean Neurol Assoc* 2017; **35**: 254–256.

48. Wan Y, Du H, Zhang L et al. Multiple cerebral metastases and metastatic aneurysms in patients with left atrial Myxoma: A case report. *BMC Neurol* 2019; **19**: 249.

49. Roque A, Kimbrough T, Traner C et al. Somatic PRKAR1A mutation in sporadic atrial myxoma with cerebral parenchymal metastases: A case report. *J Med Case Reports* 2019; **13**: 389.

50. Maas JA, Menes M, Siomin V. Cardiac Myxoma with cerebral metastases and chronic lymphocytic leukemia/small lymphocytic lymphoma: A case report and review. *J Neurol Surg Rep* 2020; **81**: e1–e6.

51. Panos LD, Brunel C, Berezowska S et al. Early and delayed neurological manifestations of cardiac myxomas. *Clin Neurol Neurosurg* 2020; **190**: 105673.

52. Markel ML, Armstrong WF, Waller BF, Mahomed Y. Left atrial myxoma with multicentric recurrence and evidence of metastases. *Am Heart J* 1986; **111**: 409–413.

53. Acikel M, Yekeler I, Ates A, Erkut B. A giant left atrial myxoma: An unusual cause of syncope and cerebral emboli. *Int J Cardiol* 2004; **94**: 325–326.

54. Raza E., Kamal A. K.. Recurrent non-aneurysmal, metastatic intraparenchymal haemorrhages following resection of atrial myxoma - case report and literature review. Case Reports. 2012; **2012**: oct24 2: bcr0220125772–bcr0220125772. <http://dx.doi.org/10.1136/bcr.02.2012.5772>.

55. Rose D, Papa A, Tomao S, Greco E, Zacharias J. Cerebral metastases in patients with left atrial Myxoma. *J Card Surg* 2016 May; **31**: 289–293.

56. Vontobel J, Huellner M, Stolzmann P. Cerebral ‘metastasizing’ cardiac myxoma. *Eur Heart J* 2016; **37**: 1680.

57. Kotani K, Matsuzawa Y, Funahashi T *et al.* Left atrial myxoma metastasizing to the aorta, with intraluminal growth causing renovascular hypertension. *Cardiology* 1991; **78**: 72–77.

58. Todo T, Usui M, Nagashima K. Cerebral metastasis of malignant cardiac myxoma. *Surg Neurol* 1992; **37**: 374–379.

59. Bernet F, Stulz PM, Carrel TP. Long-term remission after resection, chemotherapy, and irradiation of a metastatic myxoma. *Ann Thorac Surg* 1998; **66**: 1791–1792.

60. Hou Y. Recurrent cardiac Myxoma with multiple distant metastasis and malignant change. *J Formos Med Assoc* 2001; **100**: 63–65.

61. de Moraes C. Myocardial infarct due to a unique atrial Myxoma with epithelial-like cells and systemic metastases. *Arch Pathol Lab Med* 1988; **112**: 185–190.

62. New PF, Price DL, Carter B. Cerebral angiography in cardiac myxoma. *Radiology* 1970; **96**: 335–345.

63. Liao W, Ramkalawan D, Liu J, Shi W, Zee C. The imaging features of neurologic complications of left atrial myxomas. *Eur J Radiol* 2020; **84**: 933–939.

64. Sun D, Wu Y, Liu Y, Yang J. Primary cardiac myxofibrosarcoma: Case report, literature review and pooled analysis. *BMC Cancer* 2018; **18**: 1–10.

65. Aydin F. Do human intracranial arteries lack vasa vasorum? A comparative immunohistochemical study of intracranial and systemic arteries. *Acta Neuropathol* 1998; **96**: 22–28.

66. Portanova A, Hakakian N, Mikulis DJ, Virmani R, Abdalla WMA, Wasserman BA. Intracranial vasa vasorum: Insights and implications for imaging. *Radiology* 2013; **267**: 667–679.

67. Koo Y-H, Kim T-G, Kim O-J, Oh S. Multiple fusiform cerebral aneurysms and highly elevated serum interleukin-6 in cardiac Myxoma. *J Korean Neurosurg Soc* 2009; **45**: 394–396.

68. Yaguchi H, Murakami Y, Sengoku R, Sato H, Inoue K. A case of cardiac myxoma presenting with multiple cerebellar hemorrhages and elevation of interleukin-6 in the cerebrospinal fluid. *Rinsho Shinkeigaku* 2004; **44**: 677–681 (In Japanese.).

69. Ezerioha N, Feng W. Intracardiac myxoma, cerebral aneurysms and elevated interleukin-6. *Case Rep Neurol* 2015; **7**: 152–155.

70. Benbow U, Biology CB-M. The AP-1 site and MMP gene regulation: What is all the fuss about? *Matrix Biol*. 1997; **15**: 519–526.

71. Muhammad S, Planz O, Schwaninger M. Increased plasma matrix metalloproteinase-9 levels contribute to intracerebral hemorrhage during thrombolysis after concomitant stroke and influenza infection. *Cerebrovasc Dis Extra* 2016; **6**: 50–59.

72. Orlandi A, Ciucci A, Ferlosio A, Pellegrino A, Chiariello L, Spagnoli LG. Increased expression and activity of matrix metalloproteinases characterize embolic cardiac myxomas. 2005; **166**: 1619–1628.

73. Gialeli C, Theocaris AD, Karamanos NK. Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. *FEBS J* 2011; **278**: 16–27.

74. Zhu J, Pang Z, Yu Y. Regulation of trophoblast invasion: The role of matrix metalloproteinases. *Rev Obstet Gynecol*. 2012; **5**: 137–143.

75. Zhang X, Ares WJ, Taussky P, Ducruet AF, Grandhi R. Role of matrix metalloproteinases in the pathogenesis of intracranial aneurysms. *Neurosurg Focus* 2019; **47**: 1–7.

76. Partridge CR, Sampson HW, Forough R. Long-term alcohol consumption increases matrix metalloproteinase-2 activity in rat aorta. *Life Sci* 1999; **65**: 1395–1402.

77. Nikkari ST, Höyhtyä M, Isola J, Nikkari T. Macrophages contain 92-kd gelatinase (MMP-9) at the site of degenerated internal elastic lamina in temporal arteritis. *Am J Pathol* 1996; **149**: 1427–1433.

78. Ihara M, Tomimoto H, Kinoshita M *et al.* Chronic cerebral hypoperfusion induces MMP-2 but not MMP-9 expression in the microglia and vascular endothelium of white matter. *J Cereb Blood Flow Metab* 2001; **21**: 828–834.

79. Hernandez-Guillamon M, Martinez-Saez E, Delgado P *et al.* MMP-2/MMP-9 plasma level and brain expression in cerebral amyloid angiopathy-associated hemorrhagic stroke. *Brain Pathol* 2012 Mar; **22**: 133–141.

80. Lone RA, Ahanger AG, Singh S *et al.* Atrial myxoma: Trends in management. *Int J Health Sci* 2008; **2**: 141–151.