Case Report

Radio-pathological characteristics of malignant transformation of an epidermoid cyst in the cerebellopontine angle: A case report

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ABSTRACT

Background: Intracranial epidermoid cysts are rare congenital neoplasms that are clinically indolent and histologically benign. They rarely show malignant transformation, and several such cases have been reported. Some radiological features that suggest malignant transformation have been reported. However, histopathological features that indicate a high risk of malignant transformation have not been reported to date.

Case Description: We report a 59-year-old woman with a benign epidermoid cyst in the cerebellopontine angle that showed malignant transformation after 6 years. Magnetic resonance imaging (MRI) at the time of initial onset displayed a high-intensity signal on diffusion-weighted imaging (DWI), no peritumoral edema, and no enhancement on contrast-enhanced T1-weighted imaging. On the other hand, MRI at the time of malignant transformation showed a low-intensity signal on DWI, peritumoral edema, and enhancement of the tumor capsule on contrast-enhanced T1-weighted imaging. Pathological findings at the time of the first surgery differed from normal benign epidermoid cysts, in that stratified squamous epithelial metaplasia was observed, and immunohistochemical (IHC) analysis showed positive p53 staining. In addition, IHC analysis at the time of malignant transformation demonstrated positive p16 staining.

Conclusion: In benign epidermoid cysts, it is considered to cause malignant transformation when squamous metaplasia or p53 mutation is observed. Therefore, strict follow-up is required while paying attention to the characteristic changes in MRI for early detection and timely treatment of malignant transformation.

Keywords: Cerebellopontine angle, Epidermoid cyst, Malignant transformation, p16, p53, Stratified squamous epithelial metaplasia

INTRODUCTION

Intracranial epidermoid cysts are rare congenital neoplasms that are clinically indolent and histologically benign, and account for 0.2–1.8% of all intracranial tumors.[6,7,40] In addition, the malignant transformation of intracranial epidermoid cysts is extremely rare. Although there are some reports of the malignant transformation of intracranial epidermoid cysts, and reports of magnetic resonance imaging (MRI) findings that are suggestive of malignant transformation,[2,3,4,15,16,17,18,19,21,22,29,30,37,39,42,45,46,49,53,56] there are no reports to date regarding the characteristics that are associated with malignant transformation.

Here, we report a case of a patient with a cerebellopontine angle (CPA) epidermoid cyst that was determined to be squamous epithelial metaplasia and p53 mutation on histopathology at the first operation. Although the tumor was initially benign, malignant transformation was detected 6 years after the initial operation, with changes on MRI. Characteristics of the cyst that were detected upon the initial immunohistochemical (IHC) analysis were considered to be useful for predicting future malignant transformation. The data of this case before recurrence have already been published in a previous paper.[46]

CASE REPORT

History and surgical treatment

A 59-year-old woman presented with no relevant past medical history initially presented in 2012 with a 3-year history of right tinnitus, hearing disturbance, and hemifacial paresis. Her right facial function was House–Brackmann (H-B) Grade III, and hearing function was American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) class B. MRI displayed an extra-axial mass lesion with a maximum diameter of 20 mm in the right CPA. The lesion showed a low-intensity signal on T1-weighted imaging, a high-intensity signal on T2-weighted imaging, and a high-intensity signal on diffusion-weighted imaging (DWI) [Figures 1a-c]. Furthermore, the lesion showed no enhancement on contrast-enhanced T1-weighted imaging [Figure 1d]. Therefore, the MRI findings were compatible with a benign epidermoid cyst. The tumor was near-totally removed by the lateral suboccipital retrosigmoid approach.

The tumor contents were pearly white debris and could easily be aspirated [Figure 1e]. The tumor capsule was a translucent thin membrane that could easily be removed from the surrounding tissue, but a small portion of the capsule was left because it was tightly adhered to the brainstem and facial nerve (near-total removal) [Figures 1f and g]. Postoperative facial nerve function and hearing function were H-B grade V and AAO-HNS Class B, respectively. For postoperative follow-up, a neurological examination and non-contrast enhanced MRI were performed every year. Results indicating recurrence were observed on MRI 6 years after the initial surgery. On MRI at that time, the lesion showed a low-intensity signal on T1-weighted imaging, but unlike the MRI findings before recurrence, the lesion showed a heterogeneous low-intensity signal on T2-weighted imaging, and a low-intensity signal on DWI [Figures 2a-c]. Since the lesion was very small at that time, we decided to perform a shorter follow-up including contrast-enhanced MRI. However, the lesion grew rapidly within 2 years until it began compressing the brainstem, and MRI showed contrast effects of the tumor capsule on contrast-enhanced T1-weighted imaging [Figures 2d-i]. Moreover, edema around the brainstem owing to tumor compression was also observed. Cerebrospinal fluid analysis at that time showed that both the protein level and cell number were within the normal range. Based on the MRI findings, malignant transformation of the CPA epidermoid cyst was considered. In addition, as the tumor grew, the patient's hearing function deteriorated to AAO-HNS Class D, and she also developed gait disturbance. Therefore, reoperation was performed 8 years after the initial operation for the purpose of a definitive diagnosis on histopathology
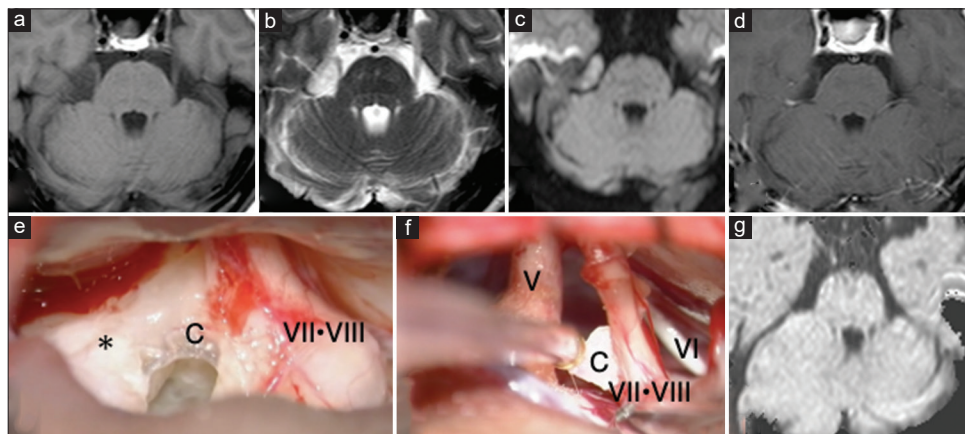
Figure 1: Magnetic resonance imaging (MRI) and intraoperative findings of a 59-year-old woman with a right cerebellopontine angle epidermoid cyst, before its malignant transformation (a-d) Preoperative MRI displayed a low-intensity signal on T1-weighted imaging, a high-intensity signal on T2-weighted imaging, and a high-intensity signal on diffusion-weighted imaging (DWI) without enhancement on contrast enhanced T1-weighted imaging. (e) The tumor contents (*) were pearly white debris, and the tumor capsule was a translucent thin membrane, most of which could be easily removed from the surrounding tissue. (f) A small portion of the capsule was left because of its tight adhesion to the facial nerve. (g) Postoperative MRI displayed no obvious residual tumor. MRI sequences in (a) is T1-weighted images. MRI sequences in (b) are T2-weighted images. MRI sequences in (c and g) are DWI. MRI sequences in (d) are contrast-enhanced T1-weighted images. C=Tumor capsule; V=Trigeminal nerve; VI=Abducens nerve; VII=Facial nerve; VIII=Vestibulocochlear nerve.

and the relief of brainstem compression. The tumor extended from above the tentorium to the jugular foramen. Therefore, the tumor was removed using the combined transpetrosal approach. Unlike the tumor that had been removed initially, this tumor contained yellowish and flaky debris and could not be easily aspirated [Figure 2j]. The tumor capsule was also a thick and cloudy membrane that tightly adhered to the surrounding cranial nerves and brainstem and was subtotally removed [Figure 2k]. Postoperative histopathological analysis demonstrated malignant transformation of the epidermoid cyst, and hence stereotactic radiotherapy (local 50 Gy in 25 fractions) was performed as postoperative adjuvant therapy. At the time of writing, 7 months have passed since the second surgery, but no regrowth has been observed.

Histopathology

At the time of the first surgery, histological analysis revealed that the cyst lining was composed of stratified squamous epithelium with a granular layer and abundant lamellated keratin flakes. The histological diagnosis was an epidermoid cyst. The cyst lining demonstrated multilayered squamous metaplasia owing to the proliferation of basal cells with mild nuclear atypia [Figure 3a]. The atypical squamous cells showed loss of cellular polarity without mitotic figures. IHC analysis revealed that these atypical squamous epithelial cells

had partial loss of staining for epithelial membrane antigen (EMA), 70–80% of the cells were positive for p53, and a few cells were positive for p16 [Figures 3b-d].

At the time of the second surgery, histological analysis revealed that the cyst lining had typical epidermoid features, and in many parts the cyst lining showed multilayered squamous metaplasia with atypical features, such as the loss of cellular polarity and few mitotic figures [Figures 3e and f]. IHC analysis revealed that almost all of the atypical squamous epithelial cells were positive for p53, and 30–40% of the cells were positive for p16 [Figures 3g and h].

DISCUSSION

Intracranial epidermoid cysts are congenital lesions caused by ectodermal cell migration during neural tube closure, at 3–5 weeks of gestation.[53] Histopathological analysis has demonstrated that the cyst lining is composed of a stratified squamous epithelium with a granular layer and abundant lamellated keratin flakes.[5,9,13,15,27,47,48] Therefore, epidermoid cysts are considered to be benign tumors. The malignant transformation of an epidermoid cyst into squamous cell carcinoma was first reported in Germany by Ernst in 1912.[12] Since then, several cases of the malignant transformation of a benign epidermoid cyst have been
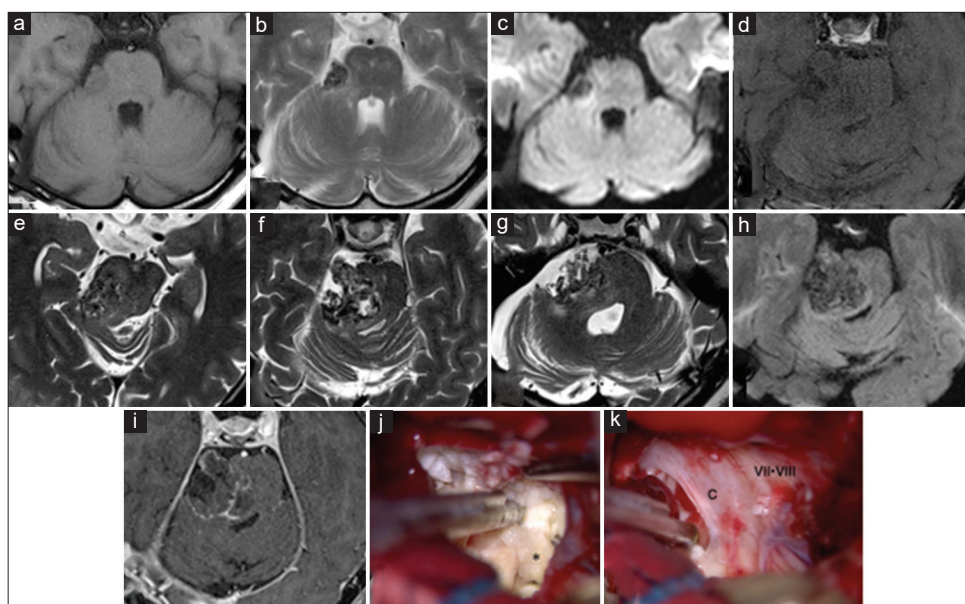
Figure 2: Magnetic resonance imaging (MRI) and intraoperative findings of a 59-year-old woman with a right cerebellopontine angle epidermoid cyst, after its malignant transformation (a-c) MRI 6 years after the initial surgery displayed slight characteristics of recurrence. The lesion showed a low-intensity signal on T1-weighted imaging, a heterogeneous low-intensity signal on T2-weighted imaging, and a low-intensity signal on DWI. (d-i) MRI 8 years after the initial surgery displayed a contrast effect on the tumor capsule, suggesting malignant transformation. (j) The tumor contents (*) were yellowish and flaky debris, unlike that of the initial surgery. (k) The tumor capsule was a thick and cloudy membrane that tightly adhered to the surrounding cranial nerves and brainstem. MRI sequences in (a and d) are T1-weighted images. MRI sequences in (b and e-g) are T2-weighted images. MRI sequences in (c) and (h) are DWI. MRI sequences in (i) is contrast-enhanced T1-weighted images. C=Tumor capsule; VII=Facial nerve; VIII=Vestibulocochlear nerve.
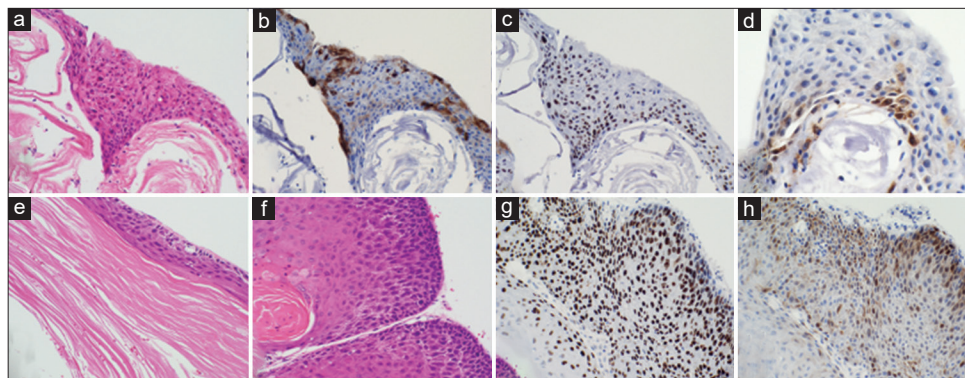
Figure 3: Histopathological findings of the tumors removed at the first (a-d) and second (e-h) surgeries (a) Hematoxylin and eosin staining showing a cyst with a lining composed of stratified squamous epithelium with a granular layer and abundant lamellated keratin flakes. The squamous epithelium shows multilayered squamous metaplasia in some regions, resulting from the proliferation of basal cells. These squamous cells show mild atypical features and loss of cell polarity (original magnification: ×200). (b-d) Immunohistochemical analysis (b: Epithelial membrane antigen (EMA), ×200; c: p53, ×200; d: p16, ×400). The stratified squamous epithelial cells show partial positive staining for EMA, and 70% to 80% of the cells were positive for p53 and 10% to 20% of the cells were positive for p16. (e and f) Hematoxylin and eosin staining showing the cyst lining composed of stratified squamous epithelium with a granular layer and abundant lamellated keratin flakes. (e) In many parts of the cyst lining, the squamous epithelium shows multilayered metaplasia of atypical squamous cells, with a few mitotic figures (e and f: original magnification ×200) (g and h) Immunohistochemical analysis (g: p53, ×200; h: p16, ×200). Almost all atypical squamous cells were positive for p53, and 30–40% of the cells were positive for p16.

reported, and are summarized in [Table 1]. There were 26 patients (10 men and 16 women), with a mean age of 54.0 years. CPA was the most common site of occurrence (61.5%), with a mean interval to malignant transformation of 82.7 months. Regarding the mechanism of malignant transformation of a remnant benign epidermoid cyst, the involvement of chronic inflammation owing to the remnant cystic components and the intraoperative introduction of foreign materials into the cyst have been suggested, but the precise mechanism of malignant transformation remains unclear to date.[1,10,18,25,34-36,38,51,54]

Imaging findings that are suggestive of the malignant transformation of a benign intracranial epidermoid cyst is the appearance of rapid growth, peritumoral edema, tissue invasion, low-intensity signal on DWI, and the appearance of new enhancement following contrast administration[11,37,42] In the present patient, no recurrence of the epidermoid cyst was observed until 6 years after the first operation, but rapid regrowth with peritumoral edema and invasion into the brainstem was observed thereafter. At that time, a change from high- to low-intensity signal on T2-weighted imaging and DWI on MRI was observed. In addition, as enhancement of the tumor capsule following contrast administration was observed, it was considered that malignant transformation had occurred. The high-intensity signal on DWI in benign epidermoid cysts is considered to be owing to the T2 shine-through effect, and the signal change to a low-intensity signal at the time of malignant transformation is considered to be a result of central necrosis in the carcinomatous part of the mass lesion.[3,23,37] Ozutemiz *et al.*[41] reported that squamous cell carcinomas are mostly heterogeneous, hypointense

on T2-weighted imaging due to high cellularity, with some hyperintensity being observed probably owing to necrosis. We also considered that the decrease in diffusion restriction owing to the increase in epithelial components and the decrease in keratin flakes contributes to the change in intensity on DWI. In our patient as well, a heterogeneous low intensity on T2-weighted imaging was observed at the time of malignant transformation. Regarding contrast effects in epidermoid cysts, as contrast effects are also seen in regions undergoing the foreign body giant cell reaction, they do not necessarily indicate malignant transformation.[32] Lakhdar *et al.*[25] reported that minimal rim enhancement occurs in approximately 25% of epidermoid cysts. A similar contrast effect was observed in the previous reports summarized in [Table 1]. Therefore, histopathological analysis of an epidermoid cyst is necessary for a definitive diagnosis of malignant transformation. In the present patient as well, reoperation was performed not only to remove the epidermoid cyst but also to make a definitive diagnosis.

At the time of reoperation, the tumor capsule was tightly adhered to the surrounding tissue, so the removal rate was lower than that at the first surgery. However, this finding is not specific to malignant transformation because the tumor capsule becomes more difficult to remove also during the reoperation of benign epidermoid cysts.[46] In this case, the lesion was very small when recurrence was observed 6 years after the initial surgery, so reoperation was not performed immediately and the patient was followed up for a short period of time. However, considering the possibility of rapid increase due to malignant transformation and the low removal rate at the time of reoperation, it was better to

Table 1: Cases of malignant transformation of a benign intracranial epidermoid cyst reported in the literature.

Authors	Year	Age/sex	Location of tumor	Changes in MRI findings before and after malignant transformation			Interval from diagnosis of a benign tumor to its malignant transformation (months)	Postoperative adjuvant therapy after malignant transformation	Outcome after malignant transformation (period)
				DWI	CE	Edema			
Fox and South[13]	1965	43/M	Temporal	n.a.	n.a.	n.a.	90	None	Death (1.5 months)
Toglia et al.[53]	1965	53/F	Base of brain	n.a.	n.a.	n.a.	12	None	Death (1 day)
Goldman and Gandy[17]	1987	59/M	Lateral ventricle	n.a.	n.a.	n.a.	396	RT	Alive (36 months)
Salazar et al.[47]	1987	49/M	CPA	n.a.	n.a.	n.a.	3	RT	Alive (10 months)
Abramson et al.[1]	1989	37/M	CPA	n.a.	n.a.	n.a.	60	None	n.a.
Nishiura et al.[39]	1989	38/M	CPA	n.a.	n.a.	n.a.	6	CRx	Alive (24 months)
Knorr et al.[22]	1991	74/M	CPA	n.a.	n.a. → +	n.a. → +	13	RT	Death (15 weeks)
Tognetti et al.[54]	1991	67/F	Frontotemporal	n.a.	n.a.	n.a.	372	None	Death (1 month)
Bayindir et al.[6]	1996	67/F	Lateral ventricle	n.a.	n.a. → +	n.a.	10	None	Alive (36 months)
Murase et al.[34]	1999	39/F	CPA	n.a.	n.a. → +	n.a.	120	CRx + SRS	Alive (60 months)
Asahi et al.[4]	2001	55/F	CPA	n.a.	n.a. → +	n.a. → -	156	None	Death (3 months)
Link et al.[27]	2002	57/F	CPA	n.a.	± → +	- → +	12	RT + SRS	Death (32 months)
Akar et al.[2]	2003	n.a./F	CPA	n.a.	n.a.	n.a.	18	None	Death (5 months)
Hamlat et al.[18]	2003	54/F	Temporal	n.a.	- → +	n.a.	10	CRx	Death (6 months)
Tamura et al.[51]	2006	64/F	Sphenoid	n.a.	→ +	- → -	96	SRS	Alive (18 months)
Ge et al.[16]	2009	44/M	Temporal	n.a.	n.a.	n.a.	74	None	n.a.
Kano et al.[21]	2010	64/F	CPA	n.a.	+ → +	- → -	192	RT	Death (25 months)
Nakao et al.[36]	2010	74/F	CPA	n.a. → Low	n.a. → +	n.a.→ -	240	RT	Alive (17 months)
Hao et al.[19]	2010	61/F	Prepontine	n.a.	- → +	n.a.	72	None	Death (1.2 months)
Lakhdar et al.[25]	2011	52/M	CPA	n.a.	+ → +	n.a.	6	RT	Alive (3 months)
Chon et al.[10]	2012	43/M	CPA	High → n.a.	- → +	- → +	5	SRS + CRx	Alive (81 months)
Vellutini et al.[56]	2014	42/F	CPA	n.a.	+ → +	n.a.	24	None	Death (1.3 months)
Pikis and Margolon[42]	2016	77/M	CPA	n.a.	- → +	n.a.	9	RT	Death (6 months)
Ding et al.[11]	2016	55/F	Temporal	High → n.a.	→ +	n.a.	n.a.	None	Death (6 months)
Mascarenhas et al.[30]	2017	35/F	CPA	n.a.	- → +	n.a.	60	None	n.a.
Solanki et al.[49]	2017	47/F	CPA	n.a.	- → +	- → +	12	None	Death (1.5 months)
Present study	2021	59/F	CPA	High → Low	→ +	- → +	108	RT	Alive (7 months)

CE: Contrast enhancement, CPA: Cerebellopontine angle, CRx: Chemotherapy, F: Female, High: High-intensity signal, Low: Low-intensity signal, M: Male, n.a.: Not available, RT: Radiotherapy, SRS: Stereotactic radiosurgery

perform the reoperation as soon as possible even if the lesion was small.

Regarding postoperative adjuvant therapy for the malignant epidermoid cysts, as a review by Kwon *et al.*[24] reported that stereotactic radiotherapy was effective, we performed the same treatment on our present patient (local, 50 Gy). At the time of writing (7 months since the second surgery), no regrowth has been detected.

The difference from the pathological findings of a typical benign epidermoid cyst at the time of initial surgery in our patient was that multilayered squamous metaplasia caused by the proliferation of basal cells with mild nuclear atypia, and loss of cellular polarity without mitotic figures were observed. In a previous report, Bayindir *et al.*[6] reported a benign epidermoid cyst that initially demonstrated a mild to moderate degree of dysplasia with some loss of polarity, hyperchromasia, and mitotic activity. In this patient, recurrence was observed after 10 months, and carcinoma *in situ* was observed on histopathological analysis of the cyst at the time of reoperation. In addition, IHC analysis of the cyst of our present patient revealed that these atypical squamous epithelium cells showed partial loss of staining for EMA, 70%–80% of the cells were positive for p53, and a few cells were positive for p16. The p53 protein was first identified in a complex with the simian virus 40 large T-antigen.[14,26,28] The p53 gene induces the repair of damaged DNA by activating repair proteins and by stopping the cell cycle at the G/S regulation point, thus arresting cell growth.[57] The p53 gene also plays a role in initiating the apoptosis of cells with irreparable DNA damage, as an anticancer gene.[31] Therefore, tumorigenic p53 mutations enable tumor cells to resist apoptosis and expand clonally.[43] In fact, p53 mutation is known to be early event in the developmental stage for a cutaneous squamous cell carcinoma due to ultraviolet light damage.[43] Although the triggers for p53 mutation may be different, p53 mutation is also likely to be an early event of malignant transformation in intracranial epidermoid cysts, which are the migration of ectodermal cells into the skull. Therefore, in our case, it is considered that the benign epidermoid cyst had a p53 mutation at some point, causing squamous metaplasia, and the residual tumor subsequently developed malignant transformation. The p16 protein is a cell cycle-associated protein coded by the tumor suppressor gene cyclin-dependent kinase inhibitor 2A, which generally activates the Rb protein family to block G1 to S-phase progression.[20,44,50,55] The TP16 mutation is found in various cancer tissues, such as squamous cell carcinoma and is considered to be a surrogate marker of dysplasia and carcinogenesis.[43,50,52,55] The role of TP16 mutations in carcinogenesis and the malignant progression of epidermoid cysts has not been clearly established, but they may be predictors of malignant transformation. Although p16 overexpression was also seen in human papillomavirus (HPV)-associated cancer, the history of HPV infection was not clear in our present patient.[8,29,33,58]

CONCLUSION

Although epidermoid cysts are benign, it is considered to cause malignant transformation when squamous metaplasia or p53 mutation is observed. Therefore, in such cases, strict follow-up is required while paying attention to the characteristic changes in MRI for early detection and timely treatment of malignant transformation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Conflicts of interest

There are no conflicts of interest.

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