Natural History of Unruptured Vertebral Basilar Artery Dissection: Temporal Changes in Imaging Findings and Contributory Factors

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Research Article

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Abstract

Purpose

To investigate temporal changes in imaging findings of conservatively treated unruptured vertebral basilar artery dissection and its contributing factors.

Methods

Fifty-three patients who underwent conservative treatment for 64 cases of vertebral basilar artery dissection diagnosed between January 2006 and March 2019 and follow-up of at least 12 months after onset were retrospectively investigated. Statistical analyses of age, sex, medical history, pattern of onset, lesion site, imaging findings and changes over time, regular medication, and outcomes were performed.

Results

Changes in the vascular morphology of the lesion site during the follow-up period were observed in only 23 (43%) patients (median time until change: 19 days). Univariate analysis of factors contributing to morphological changes at the dissection site showed that changes were significantly more likely in younger patients ($p = 0.011$). Patients taking antiplatelet drugs had a significantly greater rate of deterioration at the dissection site ($p = 0.028$) than others. On multivariate analysis, age was an independent factor contributing to changes at the dissection site, and taking antiplatelet drugs, particularly clopidogrel, was an independent factor contributing to deterioration. No patient developed intracranial hemorrhage, cerebral infarction, or worsening of neurological symptoms during follow-up.

Conclusions

Morphological changes at the dissection site are more likely in younger patients with unruptured vertebral basilar artery dissection and those taking antiplatelet drugs. However, chances of intracranial hemorrhage, cerebral infarction, or worsening of neurological symptoms during conservative therapy are low. Therefore, unruptured vertebral basilar artery dissection may be considered a benign condition.

Introduction

Cerebral artery dissection gained attention in the 1990s with the advancement in diagnostic imaging technology. Vertebral basilar artery dissection is broadly classified as ruptured or unruptured; if it ruptures, a subarachnoid hemorrhage occurs, with a high probability of rebleeding and a poor prognosis in many cases [1-3]. In recent years, the incidental discovery of unruptured vertebral basilar artery dissection has increased in patients presenting with headache or neurological symptoms due to cerebral infarction. Compared with ruptured dissections, the prognosis is said to be good, and conservative therapy is recommended for treatment [4-8]. However, much about the natural history of unruptured ventral basilar artery dissection under conservative treatment remains unclear. Moreover, since it is difficult to follow long-term changes in imaging findings and outcomes, this information remains unknown [2,8,9]. In addition, to the best of our knowledge, there have been no reports of factors contributing to changes in imaging findings of the vertebral basilar artery dissection site. Therefore, temporal changes in imaging findings of conservatively treated unruptured vertebral basilar artery dissection and factors contributing to changes were investigated in this study.

Materials And Methods

Ethics Statement

This study was approved by the Ethical Committee for Epidemiology of Hiroshima University (No. E-2562). Since personal data was anonymized and collected from medical records, and since this study does not pose any risk to patients, there was no need for individual informed consent, and an opt-out method was used to obtain informed consent for this study.

Study Design

This retrospective study included patients with unruptured vertebral basilar artery dissection who were admitted to Hiroshima University Hospital, or associated hospitals and clinics between January 2006 and March 2019.

We selected patients who had been treated conservatively and had been followed for at least 12 months. Patients for whom this was the first vertebral basilar artery dissection with known timing of onset, were included, whereas cases discovered incidentally in a brain health examination or other health checkup or for whom the timing of onset was unknown were excluded.

All study participants had undergone 3.0 Tesla magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the head, and arterial dissection was defined as any of the following: (1) long stenosis visualized as the string sign; (2) vascular dilatation and stenosis visualized as a pearl and string sign; (3) vascular dilatation visualized as a fusiform aneurysm; or (4) occlusion. All imaging results were reviewed by at least two radiologists. Differences in opinions were resolved by consensus. Imaging findings and morphological changes over time were traced over at least the following 12 months. If any changes had occurred, the timing of the change and whether the lesion site had improved or deteriorated were evaluated; improvement was defined as improvement of a stenotic region or contraction of a dilated region, and deterioration was defined as deterioration of a stenotic region, including occlusion, or further enlargement of a dilated region.

The following parameters were included in the analysis: age, sex, medical history (hypertension, diabetes mellitus, dyslipidemia, smoking, heart disease, and cerebral infarction), pattern of onset (headache or ischemia), lesion site, imaging findings and changes over time, regular medication (anticoagulants, antiplatelet drugs, HMG-CoA reductase inhibitors), and outcomes. Images were obtained from MRI and MRA performed on admission and at 1 day, 1 and 2 weeks, and 1, 3, 6, and 12 months after onset.

All patients underwent conservative therapy from the time of admission, irrespective of whether they presented with headache or ischemia. Patient systolic blood pressure was controlled, as required, to <140 mmHg with antihypertensives. Target blood pressure was defined by the American Heart Association.

Statistical analyses

R software (version 3.1.2, http://www.r-project.org/) was used for all statistical analyses. Patient background factors, including age, sex, medical history (hypertension, diabetes, dyslipidemia, smoking, heart disease, and cerebral infarction), pattern of onset (headache or ischemia), lesion site, imaging findings and changes over time, regular medication (anticoagulants, antiplatelet drugs, HMG-CoA reductase inhibitors), and outcomes were compared using the χ^2 test, with statistical significance set at p <0.05. Changes at the dissection site (improvement, deterioration, and no change) and factors contributing to these changes were investigated using a *t*-test or Fisher's exact test. Multivariate analysis was conducted using logistic regression analysis to investigate changes at the dissection site and factors contributing to these changes.

Results

The study flow chart is presented in Figure 1. Of the 64 patients with unruptured vertebral basilar artery dissection, 11 were excluded, thus 53 patients participated in the study. Of these, 21 (40%) presented with ischemia, and 32 (60%) presented with headache. None of the patients developed intracranial hemorrhage, cerebral infarction, or worsening of neurological symptoms during follow-up. Changes in the vascular morphology of the lesion site during the follow-up period were observed in 23 (43%) patients, whereas there were no changes in 30 (57%) patients. Of those lesions that changed, 16/23 (70%) improved, 3/23 (13%) enlarged and 4/23 (17%) narrowed or became occluded. The median time until a change occurred was 19 days (Figure 2).

Table 1 shows the analysis of factors contributing to the morphological changes at the dissection site. Univariate analysis showed that changes were significantly more likely to occur in younger patients (p = 0.011) (Figure 3). Multivariate analysis using the six factors of age, sex, hypertension, smoking, antiplatelet drugs, or anticoagulants as explanatory variables also showed that changes were significantly more likely to occur in younger patients (p = 0.017, odds ratio [OR] 0.94, 95% confidence interval [95% CI] 0.89–0.99).

Table 2 shows the analysis of factors causing deterioration (enlargement, progressive stenosis, or occlusion) at the dissection site. Univariate analysis showed that morphological deterioration of the lesion site was significantly more likely to occur in patients taking antiplatelet drugs, particularly those taking clopidogrel (antiplatelet drugs, p = 0.028; clopidogrel, p = 0.007).

Multivariate analysis using the six factors of age, sex, hypertension, smoking, antiplatelet drugs, or clopidogrel as explanatory factors showed that morphological deterioration of the lesion site was significantly more likely to occur in patients taking antiplatelet drugs and those taking clopidogrel (antiplatelet drugs: p = 0.044, OR 7.24, 95% CI 1.05–49.80; clopidogrel: p = 0.008, OR 15.5, 95% CI 2.04–117.0).

Discussion

In this study, we retrospectively investigated temporal changes in the imaging findings of conservatively treated unruptured vertebral basilar artery dissection, and factors contributing to these changes were investigated. In a review of images scanned during rigorous regular follow-up over a 1-year period, no patient developed intracranial hemorrhage, cerebral infarction, or worsening of neurological symptoms. Few previous studies have conducted long-term follow-up of images of unruptured vertebral basilar artery dissection over time, and very few have reported factors involved, meaning that the present study is of clinical significance [10-13].

Temporal changes in imaging findings of vertebral basilar artery dissection

Cerebral artery dissection is considered to undergo various morphological changes after onset. One study reported that of 41 patients with vertebral artery dissection presenting with occipital or neck pain, rest and antihypertensive therapy alone produced improvements within 7 days in 12/21 patients with the pearl and string sign, 2/6 with fusiform dilatation, and 8/14 with narrowing [14]. Approximately 90% of patients show changes on imaging within 3 weeks, with gradual morphological changes subsequently continuing in many cases [15]. In the present study, univariate analysis showed that changes were significantly more likely to occur in younger patients. Morphological deterioration of the dissection site was significantly more likely to occur in patients taking antiplatelet drugs, particularly clopidogrel. Multivariate analysis showed that age was an independent factor for changes at the dissection site, and the use of antiplatelet drugs, particularly clopidogrel, was an independent factor causing deterioration. Vertebral basilar artery dissection usually occurs at around age 40–50 years, and the mean age at

onset of unruptured vertebral basilar artery dissection has been reported to be 61.2 years [1,10,16-19]. It is said to be a condition that tends to occur at a comparatively young age. In this study, the younger patients (mean 53.5 ± 14.7 years) were also more likely to show morphological changes at the dissection site than than the older patients (mean 62.8 ± 10.4 years). In addition, both univariate and multivariate analyses showed that antiplatelet drug use was a significant factor in the deterioration of the morphology of the dissection site. A previous study has also reported that the use of anticoagulants and antiplatelet drugs causes the deterioration of the dissection site, causing intracranial hemorrhage, which is in line with our findings [20]. However, in the present study intracranial hemorrhage was not observed.

Most previous studies of temporal changes in the imaging findings of vertebral basilar artery dissection have addressed patients with unruptured dissections. Moreover, many studies stated that these findings improved in most patients; however more recent studies have reported that they remain unchanged in most patients, which was also observed in the participants of this study [8,10,15,19,21,22]. Although the reason for this is unclear, it may be related to differences in the characteristics of scanning equipment, since most patients were previously monitored using cerebral angiography, whereas nowadays using MRI/MRA is more prevalent.

Timing of changes in imaging findings in vertebral basilar artery dissection

With respect to the timing of changes in imaging findings of the dissection site, aneurysm formation or stenotic lesion extension occurs in association with the progression of dissection and is apparent early on, within 3 weeks of onset, whereas morphological improvement occurs in association with the stabilization of the vascular wall by thrombus organization, and it usually occurs around 1–3 months after onset [4,15,23,24]. According to one study, vascular occlusion as a result of dissection became re-apparent within 8 days in 30% of cases and within 3 months in 60%–80% of cases [25].

Pathologically, cerebral artery dissection has an unstable structure soon after onset, but with the passage of time, the pathological appearance of the aneurysm shows spontaneous recovery of the tunica intima, progressing circumferentially until the repair is complete after approximately 2 months and the patient is clinically stable [16]. In the present study, the median time to the appearance of changes in the morphology of the dissected vessel was 19 days, which is similar to those previously reported. The fact that the imaging findings at the dissection site tend to change over a short time during the acute phase means that repeated imaging investigations are indicated [4,15,23,24].

Prognosis for unruptured vertebral basilar artery dissection

Unruptured vertebral basilar artery dissection has been widely reported to have a relatively good prognosis, and rarely develops into a serious condition [4,6,8,10,11,15,21]. Although there have been few reports of long-term follow-up, one study that monitored patients for more than 5 years reported that 78% had good outcomes [26]. In this study, although signs of deterioration of the dissection site appeared on imaging in some patients, their subsequent courses were stable, and no patient developed intracranial hemorrhage, cerebral infarction, or worsening of neurological symptoms during follow-up, a result similar to those of previous reports.

Treatment of unruptured vertebral basilar artery dissection

To date, there is no consensus on treatment strategies for unruptured vertebral basilar artery dissection. Antithrombotic and anticoagulant therapies for patients with cerebral infarction are controversial [20]. In some cases, subarachnoid hemorrhage may occur in the acute phase after administration [20]. In the event of arterial dissection,

however, the inner surface of the vascular lumen becomes smooth as a result of the repaired intima, and with this structure, thrombi are unlikely to form. It has also been shown that the risk of recurrent cerebral infarction or arterial dissection is low after 3–6 months [27,28]. Antiplatelet and anticoagulant therapies are therefore particularly recommended to prevent recurrence only during the period from 3 to 6 months after onset [27,29]. If possible, imaging investigations should be conducted every 3 months, and the necessity of antiplatelet or anticoagulant therapy and the choice of drug should be considered based on the resulting findings. In principle, if signs of stenosis at the dissection site are still present after at least 6 months, drugs should be continued. If imaging findings have completely normalized, and the dissection site has ceased to show further changes, it may be appropriate to consider discontinuing medications [1,16-19,27,28].

Limitations

Since our study was not a randomized controlled trial and the number of cases studied was not large, further accumulation of cases of arterial dissection and further analysis of the factors involved are necessary. In addition, since this study focused on non-hemorrhagic onset vertebrobasilar artery dissection, arterial dissection of the anterior circulation and hemorrhagic onset cases should also be considered. Since the follow-up of the images was performed with MRI and MRA, the study should have also considered cerebral angiography and contrast-enhanced CT.

Conclusion

Younger patients with unruptured vertebral basilar artery dissection and those taking antiplatelet drugs are more likely to show morphological changes at the dissection site. However, the probability that intracranial hemorrhage, cerebral infarction, or worsening of neurological symptoms will occur during conservative therapy is low, and therefore, unruptured vertebral basilar artery dissection may be considered a benign condition. The results of our study suggest that more careful and regular imaging follow-up is necessary for younger patients and those taking antiplatelet medication, keeping in mind the morphological changes in the dissection area.

Declarations

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considered necessary because the information was anonymized and the postings did not contain any personally identifiable images.

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Tables

Table 1. factors contributing to morphological change at the dissection site

				Univariate analysis			Multivariate analysis		
	Total (N = 53)	No change (N = 30)	Change (N = 23)						
Factor				OR	95% CI	P value	OR	96% CI	P value
Age (years)		62.8 ± 10.4	53.5 ± 14.7			0.011*	0.94	0.89 - 0.99	0.017*
Sex				0.701	0.17 - 2.85	0.754	0.622	0.14 - 2.75	0.531
Male	39	23	16						
Female	14	7	7						
Side				1.625	0.46 - 5.93	0.567			
Right	27	14	13						
Left	26	16	10						
Onset				0.552	0.15 - 1.92	0.397			
Headache	32	20	12						
Ischemia	21	10	11						
Medical history									
Hypertension	35	21	14	0.672	0.18 - 2.45	0.565	1.12	0.28 - 4.51	0.875
Diabetes mellitus	8	6	2	0.387	0.03 - 2.48	0.441			
Dyslipidemia	20	9	11	2.107	0.60 - 7.70	0.255			
Smoking	18	9	9	1.488	0.41 - 5.48	0.565	1.73	0.44 - 6.88	0.435
Ischemic heart disease	4	3	1	0.415	0.01 - 5.59	0.624			
Drug history									
Antiplatelet	17	10	7	1.748	0.47 - 6.65	0.384	3.12	0.74 - 13.20	0.121
Aspirin	11	6	5	1.109	0.23- 5.16	1			
Clopidogrel	8	2	6	4.479	0.75 - 53.77	0.065			
Cilostazol	2	2	0	0	0.00 -	0.499			

					6.94				
Anticoagulant	10	4	6	2.257	0.46 - 12.59	0.3	2.3	0.43 - 12.40	0.331
Statin	19	8	11	2.475	0.69 - 9.34	0.151			
Radiographic findings									
Fusiform dilatation	23	13	10	1.005	0.29 - 3.44	1			
Pearl and string sign	13	8	5	0.768	1.66 - 3.23	0.756			
String	11	4	7	2.786	0.59 - 15.15	0.177			
Occlusion	6	5	1	0.232	0.04 - 2.31	0.217			
location									
V	42	26	16	0.358	0.07 - 1.68	0.177			
B	2	1	1	1.311	0.02 - 106.89	1			
VP	7	2	5	3.789	0.54 - 43.83	0.218			
BP	1	0	1	-	-	0.434			
VB	1	1	0	0	0.00 - 50.82	1			

V: vertebral artery, B: basilar artery, VP: vertebral artery and posterior inferior cerebellar artery, BP: basilar artery and posterior inferior cerebellar artery, VB: vertebral artery and basilar artery, OR: odds ratio, CI: confidence interval, *: P value < 0.05

Table 2. factors causing deterioration (enlargement, progressive stenosis, or occlusion) at the dissection site

				Univariate analysis			Multivariate analysis		
	Total (N = 53)	No Change + improve (N = 46)	Change worsening (N = 7)						
Factor				OR	95% CI	P value	OR	96% CI	P value
Age (years)		58.1 ± 13.4	63.4 ± 12.1			0.819	1.04	0.96 - 1.12	0.356
Sex				0.216	0.03 - 1.50	0.069	0.204	0.03 - 1.51	0.12
Male	39	36	3						
Female	14	10	4						
Side				0.721	0.09 - 4.83	1			
Right	26	23	3						
Left	27	23	4						
Onset				0.552	0.15 - 1.92	1			
Headache	21	18	3						
Ischemia	32	28	4						
Medical history									
Hypertension	35	31	4	0.651	0.09 - 5.01	0.678	0.832	0.11 - 6.22	0.858
Diabetes mellitus	8	8	0	0	0.00 - 4.10	0.577			
Dyslipidemia	20	17	3	1.273	0.17 - 8.55	1			
Smoking	18	16	2	0.754	0.06 - 5.27	1	2.33	0.25 - 21.70	0.459
Ischemic heart disease	4	3	1	2.338	0.04 - 35.37	0.443			
Drug history									
Antiplatelet	17	12	5	6.779	0.95 - 79.9	0.028*	7.24	1.05 - 49.80	0.044*
Aspirin	11	9	2	1.627	0.13 - 12.17	0.626			
	8	4	4	12.787	1.58 -	0.007*	15.5	2.04 -	0.008*

Clopidogrel					123.82		117.00
Cilostazol	2	2	0	0	0.00 - 36.83	1	
Anticoagulant	10	9	1	0.689	0.01 - 6.93	1	
Statin	19	15	4	2.698	0.40 - 20.84	0.234	
Radiographic findings							
Fusiform dilatation	23	19	4	1.871	0.28 - 14.29	0.451	
Pearl and string sign	13	12	1	0.477	0.01 - 4.62	0.667	
String	11	9	2	1.627	0.13 - 12.17	0.626	
Occlusion	6	6	0	0	0.00 - 6.11	0.582	
location							
V	42	37	5	0.614	0.08 - 7.44	0.626	
B	2	2	0	0	0.00 - 36.83	1	
VP	7	5	2	3.182	0.24 - 27.57	0.227	
BP	1	1	0	0	0.00 - 255.26	1	
VB	1	1	0	0	0.00 - 255.26	1	

V: vertebral artery, B: basilar artery, VP: vertebral artery and posterior inferior cerebellar artery, BP: basilar artery and posterior inferior cerebellar artery, VB: vertebral artery and basilar artery, OR: odds ratio, CI: confidence interval, *: P value < 0.05

Figures

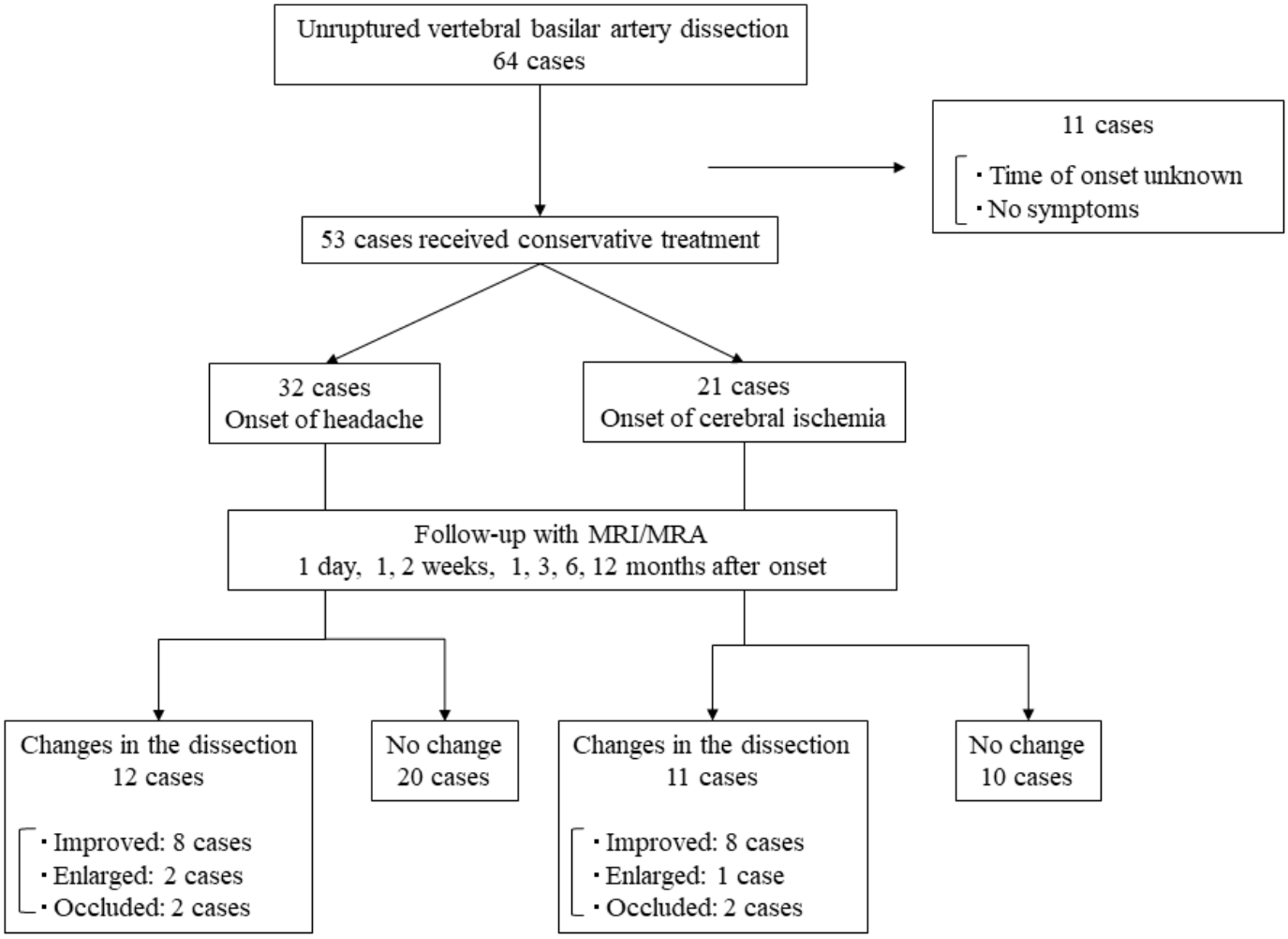

Figure 1

Flow chart of the study. A total of 64 patients with unruptured vertebral basilar artery dissection were enrolled and 53 were investigated for at least 12 months.

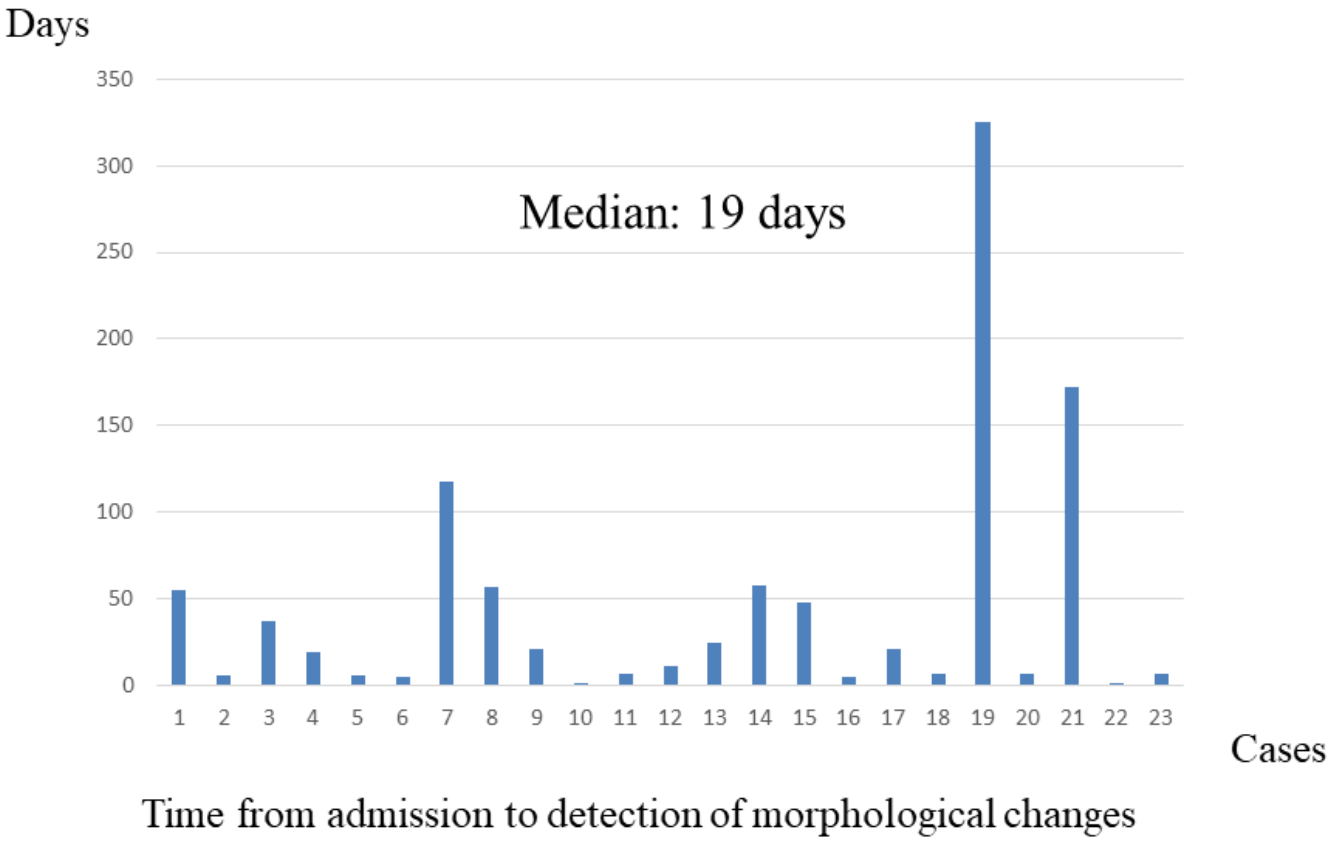

Figure 2

Graph of the time at which morphological changes appeared at the dissection site. Changes in the vascular morphology of the lesion are observed in 23 patients during the follow-up period. The median time until change occurred was 19 days.

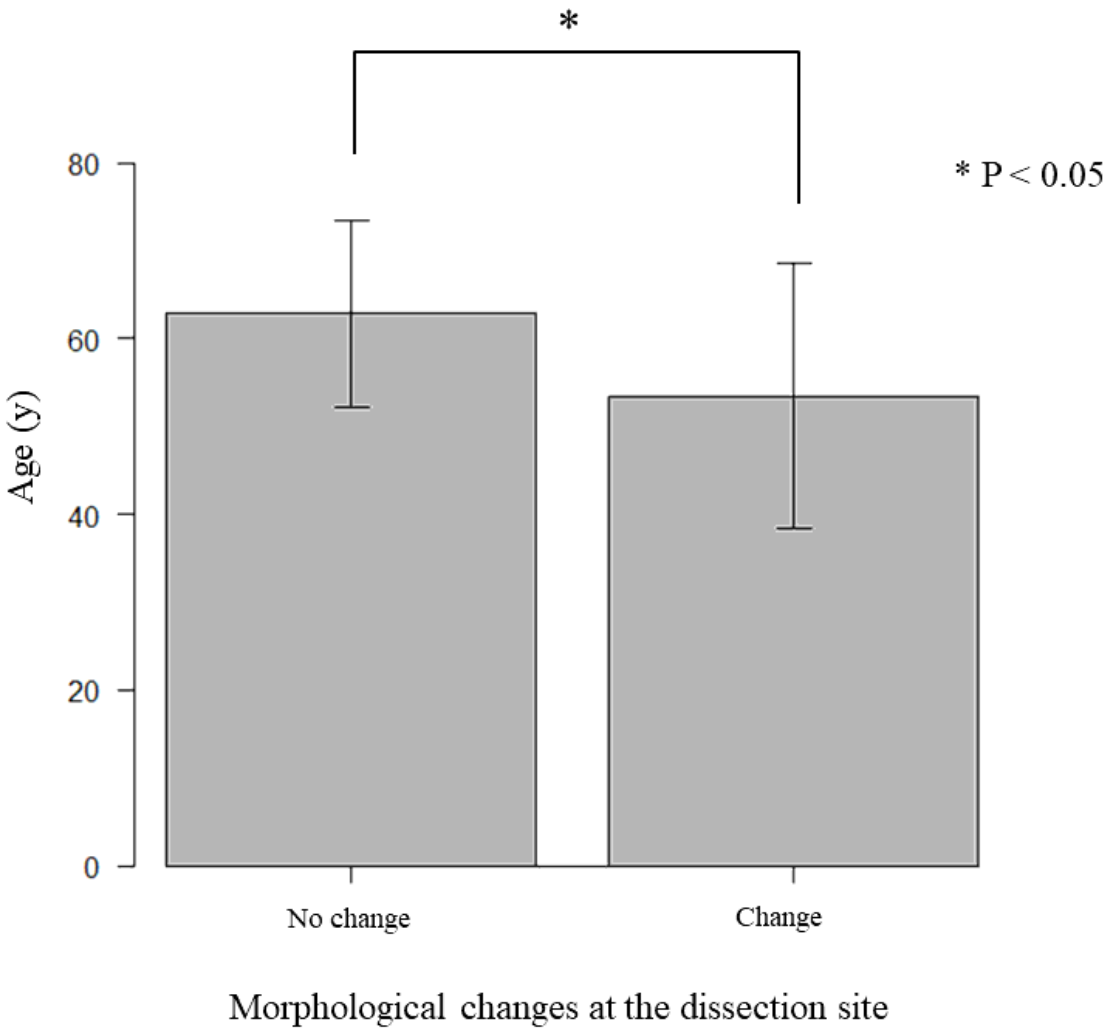

Figure 3

Relationship between morphological changes at the dissection site and age. On both univariate and multivariate analyses, changes are significantly more likely to occur in younger patients.