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Investigation of a Correlation between Thoracic Vertebra Hyperplasia and Relapse in Paroxysmal Atrial FIbrillation Patients Following Extended Pulmonary Vein Isolation

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Pulmonary vein isolation (PVI) with radio-frequency catheter ablation (RFCA) is effective therapy for the patients with paroxysmal atrial fibrillation (pAF). However, it is not easy to predict relapse of pAF. Approximately 70% pAF patients were maintained sinus rhythm for 1 year after PVI in Japan. In this study, all of the cases were underwent chest computed tomography (CT) to check for the morphology and positional relationship of the left atrium. We detected relapse cases that exhibited spur formation in the thoracic vertebrae. Therefore, we conducted an investigation based on the hypothesis that, "Because hyperostosis involves proliferative changes in the synovium or pia mater cells with an inflammatory basis, it is related to the onset of atrial fibrillation." The study sample consisted of 24 sequential cases (males: 20, mean age: 66.2 ± 6.9 years) of drug-resistant pAF that underwent PVI at our hospital between January and May, 2015. When subjects were divided into a relapse group and a non-relapse group and 21 background factors were compared, it was found that the relapse group subjects were older than the non-relapse group subjects (70.3 ± 7.2 vs 64.1 ± 5.7, p = 0.04). The proportion of cases with thoracic vertebra hyperplasia was markedly high in the relapse group (6 cases [75%] vs. 3 cases [18%], p = 0.007). No statistically significant differences were observed between the two groups for any other background factors. Our results suggested that thoracic vertebra hyperplasia could be a marker for predicting relapse after PVI in pAF patients.

Key words: Diffuse skeletal hyperostosis, pulmonary vein isolation, metabolic disorder, insulin-like growth factor-1

INTRODUCTION

With the increasing aging of society, the prevalence of atrial fibrillation is also rising rapidly. Underlying diseases that are often accompanied by atrial fibrillation include mitral valve disease, heart failure, cardiac infarction, hypertension, diabetes and hyperthyroidism [1, 2]. In an investigation based on the health checkup data of 28,449 cases, the metabolic syndrome-related diseases of obesity, hypertension, glucose tolerance disorder and hypo-HDL cholesterolemia were found to be related to the onset of atrial fibrillation [3]. Therefore, it was shown that in addition to electrical physiological dysfunction, oxidative stress related to inflammatory cytokines also contributes to the onset of atrial fibrillation. Electrical and structural remodeling in atrial fibrillation patients ultimately causes atrial dysfunction [4], and pulmonary vein isolation (PVI) using radio-frequency catheter ablation (RFCA) is useful when aiming to completely cure the condition before the onset of reversible changes. However, sinus rhythm was maintained for 1 year postoperatively following PVI in only approximately 70% of paroxysmal atrial fibrillation (pAF) cases in Japan, with relapse being observed in approximately 30% of patients [5]. Predictive factors for atrial fibrillation relapse following PVI include hypertension, left atrial diameter, left atrial low voltage area, $CHADS_2$ score and CHA_2DS_2-VASc score [6–11]. However, these factors do not offer sufficient predictive accuracy.

At our facility, chest computed tomography (CT) is routinely performed as preoperative testing for PVI to grasp atrial morphology and positional relationship in advance. As a result of this testing, some patients who suffered atrial fibrillation relapse following PVI were found to exhibit spur formation in the thoracic vertebrae. Therefore, we formulated the hypothesis that, "Because hyperostosis involves proliferative changes in the synovium or pia mater cells with an inflammatory basis, it is related to the onset of atrial fibrillation." The purpose of the present study was to demonstrate a correlation between thoracic vertebra hyperplasia and relapse in pAF patients following extended PVI.

PATIENTS AND METHODS

1. Study Patients

The study sample consisted of 24 sequential cases (males: 20, mean age: 66.2 ± 6.9 years) of drug-resistant pAF that underwent PVI at our hospital between January and May, 2015. The subjects were divided into a relapse group and a non-relapse group based on whether or not they suffered atrial fibrillation

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relapse and the following 21 background factors were retrospectively investigated: age, sex, body mass index, history of heart failure, hypertension, diabetes, history of cerebral infarction, $CHADS_2$ score, paroxysmal atrial fibrillation duration, C-reactive protein, brain natriuretic peptide (BNP), left atrial diameter, left ventricular ejection fraction (LVEF), ratio of left ventricular inflow velocity and atrial filling velocity (E/A), E wave deceleration time (EDT), thoracic vertebra hyperplasia, presence/absence of a low voltage area in the left atrium, area of low voltage area in the left atrium, presence/absence of re-conduction, time required for PVI and postoperative antiarrhythmic agents.

Echocardiography Artida (Toshiba Medical Systems, Tokyo, Japan) was used for the accurate testing of organic heart disease, and M mode long axis images were used to measure left atrial diameter and LVEF. E/A and EDT were calculated to evaluate ventricular diastolic function. To assess thoracic vertebra hyperplasia, we used thoracic CT images taken within 1 month preoperatively with CT scanner (SOMATOM Definition Flash, Siemens healthcare, Forchheim, Germany). When osteolysis projecting onto the spine was observed in at least one site on the upper or lower border of a thoracic vertebral body, this was considered to indicate the presence of hyperostosis and the case was then re-evaluated by a specialized orthopedic surgeon. In hyperostosis cases, if ossification with four consecutive vertebral and intervertebral disc degenerative diseases was confirmed, this was diagnosed as diffuse idiopathic skeletal hyperostosis (DISH) [12]. In such cases, rheumatic diseases and inflammatory bowel disease were excluded. This study was approved by the clinical study institutional review board.

2. Pulmonary vein isolation and paroxysmal atrial fibrillation relapse evaluation

For catheter ablation, the EnSite NavX System (St. Jude Medical, St Paul, Minnesota) and irrigation catheter (Flex Ability® ; St.Jude Medical, St Paul, Minnesota) were used. To treat atrial fibrillation, punctuate cauterization was applied for 30 seconds at 20W output to the posterior wall side of the left pulmonary vein and for 30 seconds at 30W output for other regions. Then, extended PVI was performed on the same side. Finally, after confirming electrical isolation of the pulmonary vein on both sides, adenosine triphosphate was used to evaluate pulmonary vein re-conduction. If re-conduction had occurred, repeat isolation was implemented using additional electrical conduction. For extended treatment of atrial flutter, transverse linear cauterization of the tricuspid valve isthmus was performed, thereby creating a bidirectional block line. To predict delays in conduction, which forms the basis within the left atrium, a voltage map was used to identify low voltage regions, the areas of which were then measured. The standard for low voltage was set at a wave crest value of 0.5 mv or lower and figures were rendered on a color scale. Purple regions indicated sites of electrical potential wave height of 0.5 mV or greater, with regions of lower values exhibiting color changes according to wave height in the form of blue → yellow → red → white.

Atrial fibrillation relapse was defined as atrial fibrillation or atrial tachycardia being maintained for 30 seconds or longer according to 24-hour Holter electrocardiography (ECG; RAC-2503, NihonKoden, Tokyo, Japan) or arrhythmia being detected on 12-lead ECG (ECG-1550, Nihon Koden, Tokyo, Japan). Assessments were performed independently by two arrhythmia specialists. Examinations of 24-hour Holter electrocardiography or 12-lead ECG were performed 3–6 months postoperatively (mean: 107 ± 65.6 days) to detect the recurrence of atrial fibrillation following extended PVI.

3. Statistical Analysis

Continuous variables are expressed as mean ± SD, and percentage. Statistical significance was assessed using the unpaired Student's t-test. Categorical variables, expressed as numbers or percentages, were analyzed with the chi-square test. All tests were 2-tailed and a P-value < 0.05 was considered statistically significant. The statistical analysis software used was commercially-available JMP® 11 (SAS Institute Inc., Cary, NC, USA).

RESULTS

1. Patient Characteristics

Subjects were divided into two groups based on whether they suffered postoperative atrial fibrillation relapse (relapse group: 8 cases, non-relapse group: 16 cases). Of the 8 cases in the relapse group, 6 cases were detected with 12-lead ECG and 2 cases were detected with Holter ECG. Comparison between the two groups of 21 background factors indicated statistically significant differences for the two factors of age and thoracic vertebra hyperplasia (Table 1). Subjects in the relapse group were older than subjects in the non-relapse group (70.3 ± 7.2 vs 64.1 ± 5.7, $p = 0.04$). The proportion of subjects with thoracic vertebra hyperplasia in the relapse group was markedly higher than in the non-relapse group (6 cases [75%] vs. 3 cases [18%], $p = 0.007$). Of the cases that exhibited hyperostosis, 3 cases in the relapse group and 1 case in the non-relapse group were diagnosed with DISH. No statistically significant differences were noted between the groups for sex, body mass index, history of heart failure, hypertension, diabetes, history of cerebral infarction, $CHADS_2$ score, paroxysmal atrial fibrillation duration, C-reactive protein, BNP, left atrial diameter, LVEF, E/A, EDT, presence/absence of a low voltage area in the left atrium, area of low voltage area in the left atrium, presence/absence of re-conduction, time required for PVI and postoperative antiarrhythmic agents.

2. Breakdown of Hyperostosis Severity in the Relapse Group

Table 2 shows, from the left, the number of impaired vertebrae according to the severity of hyperplasia in the 8 cases in the relapse group. There were 6 cases that exhibited thoracic vertebra hyperplasia, and 3 of these cases were diagnosed with DISH. At first, no large differences in background factors were apparent in the 3 cases diagnosed with DISH (Case 1, 2, 3), the 3 cases that had hyperplasia but were not diagnosed with DISH (Case 4, 5, 6), and the 2 cases that did not exhibit hyperplasia (Case 7, 8). However, the 4 cases

Table 1 Clinical Characteristics of Patients in the Relapse group and Non-Relapse group

	Relapse group (n = 8)	Non-Relapse group (n = 16)	*P* value
Age, years	70.3 ± 7.3	64.1 ± 5.8	0.04 *
Male, n (%)	7 (87)	13 (81)	0.69
Body mass index (kg/m^2)	22.2 ± 2.7	22.9 ± 2.4	0.55
Congestive heart failure, n (%)	0	0	−
Hypertension, n (%)	3 (37)	8 (50)	0.56
Diabetes mellitus, n (%)	1 (12)	2 (12)	0.72
History of stroke/TIA, n (%)	0	1 (6)	0.65
Mean $CHADS_2$ score	0.8 ± 0.82	0.8 ± 0.82	1.00
Duration of paroxysmal atrial fibrillation (month)	12.2 ± 14.5	15.0 ± 17.0	0.71
C-reactive protein (mg/dl)	0.09 ± 0.02	0.13 ± 0.07	0.22
Brain natriuretic peptide (pg/dl)	104.4 ± 79.3	66.5 ± 46.6	0.06
Left atrium diameter (mm)	38.7 ± 6.6	38.6 ± 6.1	0.98
Left ventricular ejection fraction (%)	67.5 ± 4.9	71.4 ± 7.2	0.53
Peak E/A wave ratio	1.9 ± 1.3	1.1 ± 0.3	0.06
E wave deceleration time (msec)	224.2 ± 29.6	218.5 ± 42.9	0.76
Thoracic vertebra hyperplasia, n (%)	6 (75)	3 (18)	0.007 **
Exist of low voltage zone, n (%)	3 (37)	3 (18)	0.31
Low voltage zone area (cm^2)	0.8 ± 1.1	0.4 ± 1.0	0.46
Dormant conduction, n (%)	5 (62)	5 (31)	0.07
Total procedure time (min)	36.2 ± 10.2	30.2 ± 8.2	0.15
Anti-arrhythmic drugs after RFCA, n (%)	8 (100)	15 (93)	0.47

TIA, transient ischemic attack. $CHADS_2$, Congestive heart failure; Hypertension; Age ≧75; Diabetes mellitus; and TIA. E/A, early diastolic filling velocity and atrial filling velocity ratio. RFCA, radio frequency catheter ablation. Data are presented as mean ± SD, Unpaired Student's t-test or $\chi 2$ test was used for statistical analysis. Significance level: * $p < 0.05$, ** $p < 0.01$.

Table 2 Detailed Information of Patients in the Relapse group

	Thoracic vertebra hyperplasia						Non-hyperplasia	
	DISH (+)			DISH (-)				
Case	1	2	3	4	5	6	7	8
Total number of disorder thoracic vertebra	7	7	5	3	3	1	-	-
Age, years	70	66	65	78	80	56	73	74
Sex	male	male	male	male	male	male	male	female
Body mass index (kg/m^2)	27.1	18.9	23.0	19.8	24.7	23.8	20.8	19.5
Duration of paroxysmal atrial fibrillation (month)	48	3	4	3	18	8	2	12
Congestive heart failure	-	-	-	-	-	-	-	-
Hypertension	+	-	-	+	+	-	-	-
Diabetes mellitus	-	-	-	-	-	-	-	+
History of stroke/TIA	-	-	-	-	-	-	-	-
$CHADS_2$ score	1	0	0	2	2	0	0	1
C-reactive protein (mg/dl)	< 0.09	< 0.09	< 0.09	< 0.09	< 0.09	< 0.09	< 0.09	< 0.09
Brain natriuretic peptide (pg/dl)	54	108	66	277	182	158	42	37
Left atrium diameter (mm)	41	23	41	46	39	44	40	36
Left ventricular ejection fraction (%)	67	71	70	61	79	69	65	69
Peak E/A wave ratio	1.51	0.86	NA	0.7	1.27	1.6	2.24	4.87
E wave deceleration time (msec)	180	240	NA	280	210	240	210	210
Exist of low voltage zone	+	-	-	-	+	-	-	+
Low voltage zone area (cm^2)	3	0	0	0	1	0	0	2
Dormant conduction	-	+	+	+	+	-	+	-
Total procedure time (min)	48.5	19.0	52.5	30.5	39.0	36.0	37.5	27.0
Anti-arrhythmic drugs after RFCA	+	+	+	+	+	+	+	+

DISH, diffuse idiopathic skeletal hyperostosis. TIA, transient ischemic attack. $CHADS_2$, Congestive heart failure; Hypertension; Age ≧75; Diabetes mellitus; and TIA. E/A, early diastolic filling velocity and atrial filling velocity ratio. RFCA, radio frequency catheter ablation.

with BNP of 100 pg/dl or higher were in the hyperplasia group. While, in addition to contractile dysfunction, a diverse mix of mechanisms including myocardial ischemia, increased left ventricular pressure and extensive stimulation of the atrial wall are involved in BNP elevation, it does sensitively reflect increased left ventricular filling pressure caused by diastolic failure. In 3 of the 4 cases with high BNP, diastolic dysfunction reflected in E/A and EDT was observed. For each of these cases, the paroxysmal atrial fibrillation duration was less than 12 months and their age was not limited to 75 years or older. Therefore, it appeared that high BNP had little correlation with disease duration or age.

3. A Relapse Group Case with Severe Thoracic Vertebra Hyperplasia

The case, a 70-year-old man, with an MD and PhD (Table 2, Case 1), was being treated on an outpatient basis for pAF in addition to hypertension and hyperlipidemia. His atrial fibrillation had lasted for approximately 10 months and his body mass index was 27.1, indicating obesity. His BNP was mildly elevated, at 53.4 pg/dl. Preoperative axial chest CT images revealed severe calcification on the right anterior side of the 9th thoracic vertebra on accompanied by bone projection with irregular borders impacting the right posterior wall side of the left atrium (Fig. A). Coronal images revealed bony spur and intervertebral joint adhesion in seven vertebrae from the 6th to 12th vertebra. The diagnostic criteria for DISH were met, and the intervertebral space was maintained and there were no findings indicating vertebral bone destruction or inflammation of the sacroiliac joint or vertebral areas.

A voltage map of the 3D mapping system used during catheter ablation is shown in Fig. B. Many local low voltage areas ranging from red to yellow were observed amongst the areas of normal voltage shown in purple. Results suggested that the atrial fibrillation substrate originally involves diffuse electrical dysfunction throughout the entire left atrium. The area circled in white shows the region impacted by a vertebral spur near the pulmonary vein at the right of the posterior wall of the left atrium. This was found to be a low voltage area, suggesting the presence of excitation conduction delay.

DISCUSSION

The present study investigated the relationship between atrial fibrillation relapse following pulmonary vein isolation and thoracic vertebra hyperplasia in paroxysmal atrial fibrillation patients. Generally, thoracic vertebra hyperplasia is not recognized to be the cause of the paroxysmal atrial fibrillation. As far as the authors are aware using PubMed (biomedical literature from MEDLINE provided through National Library of Medicine), SCOPUS (abstract and citation database of peer-reviewed literature), this is the first report to investigate this topic. From the result obtained from this study, investigation of differences in background factors between the relapse and non-relapse groups revealed that the relapse group subjects were older than the non-relapse group subjects (70.3 ± 7.2 vs 64.1 ± 5.7, $p = 0.04$). A new finding was the fact that the proportion of thoracic vertebra hyperplasia cases in the relapse group was markedly high in the non-relapse group (6 cases [75%] vs 3 cases [18%], $p = 0.007$).

Post-pulmonary Vein Isolation Relapse Predictive Factors

Arya *et al.* [13] analyzed the results of Holter ECG for 674 patients with paroxysmal or persistent atrial fibrillation to investigate relapse after they had undergone extended PVI. They also investigated the patients' status directly after isolation and 3, 6 and 12 months postoperatively. The atrial fibrillation relapse rate was 24.3%. Multivariate analysis was performed with relapse directly after isolation defined as "early relapse" and any relapse that occurred after that referred to as "late relapse." Results indicated that atrial diameter of 50 mm or greater was a predictive factor for early relapse (LR 5.1: 95% CI 2.0–2.9, $p = 0.002$). Meanwhile, results indicated that there were three predictive factors for late relapse. These were atrial diameter of 50 mm or greater (LR 4.6: 95% CI 2.6–9.1, $p = 0.0001$), early relapse (LR 4.3: 95% CI 2.0–9.1, $p = 0.0001$) and hypertension (LR 3.3: 95% CI 1.4–7.5, $p = 0.003$).

D'Ascenzo *et al.* [14] conducted a meta-analysis of 19 existing reports to investigate ablation treatment outcomes, complications and relapse predictive factors. The subject sample consisted of 4,357 pAF patients, 1,083 persistent atrial fibrillation patients and 1,777 chronic atrial flutter patients. The atrial fibrillation relapse rate in the mean 22 month (13–28 months) observation period following ablation was 31.2% (24.87–34.81; CI 99%) and the relapse rate for observation periods of 30 months or longer was 34.0 % (32.11–37.83; CI 99%). The three relapse predictive factors revealed were valvular atrial fibrillation (OR 5.20; 2.22–9.50; CI 95%), left atrial diameter of 50 mm or larger (OR 5.10; 2.00–12.90; CI 95%) and relapse within 30 days of surgery (OR 4.30; 2.00–10.80; CI 95%).

Based on the relatively new research results of the two reports mentioned above, it can be said that left atrial diameter of 50 mm or greater and early relapse are two factors that make the long-term maintenance of sinus rhythm after ablation difficult. Because the study samples included many persistent atrial fibrillation patients, it is possible that dysfunction and morphological changes accompanying electrical and structural remodeling of the atrium are involved in relapse. To completely cure the condition, it is best that ablation is performed when the atrial fibrillation duration is still short and left atrial volume is within the normal range.

In our study, however, despite the fact that patients were in the relatively early stages, with atrial fibrillation duration of 14 ± 16.3 months and atrial diameter of 38 ± 6.3 mm, the postoperative relapse rate (33.3%) was comparable to that of chronic atrial fibrillation patients. This suggested that even in cases with no structural abnormalities, there are some modifying factors that differ to previously reported relapse factors.

The Hyperostosis Mechanism and Atrial Fibrillation Onset

One effect of aging on hyperplasia is the fact that bone structural components decrease with age, leading to decreased bone quantity and increased susceptibility

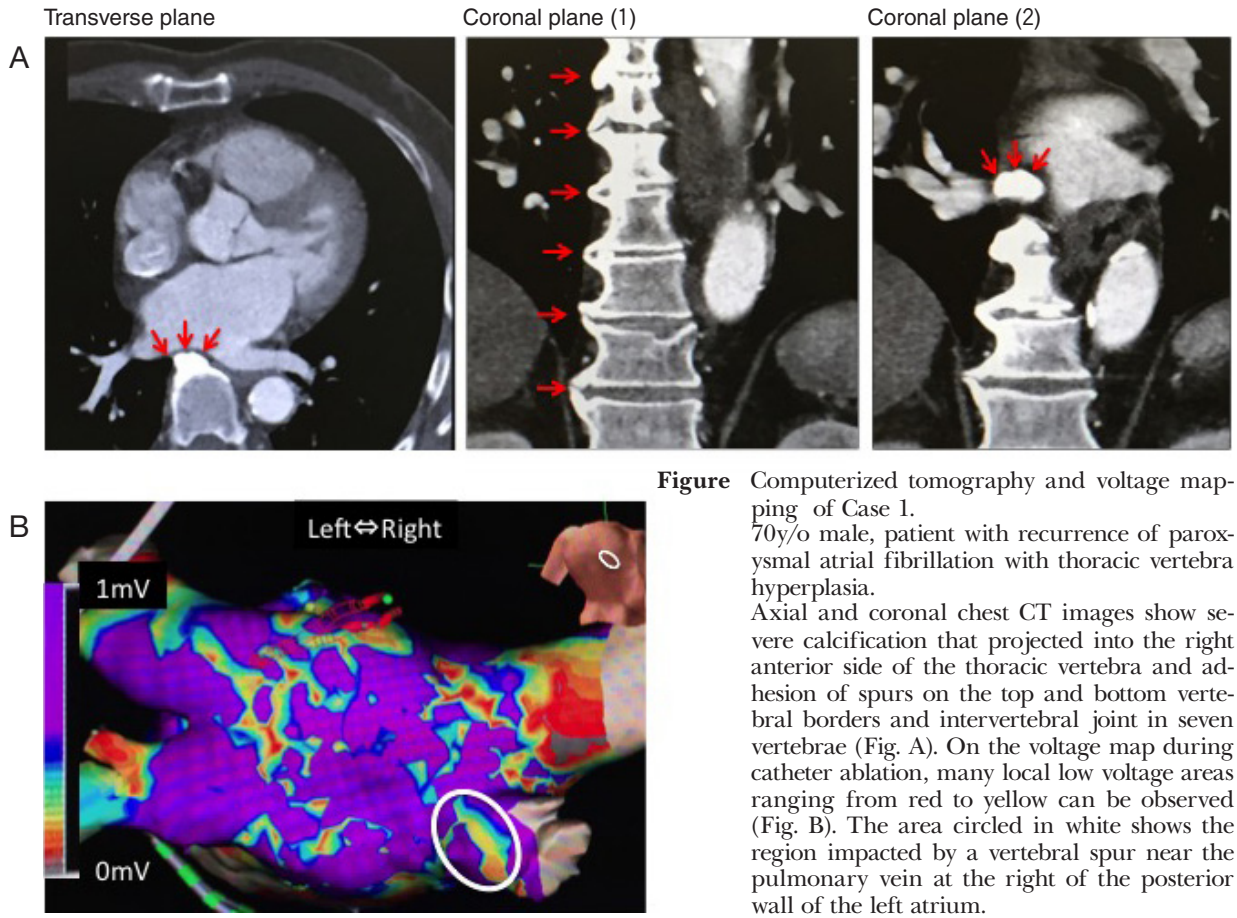

Figure Computerized tomography and voltage mapping of Case 1.
70y/o male, patient with recurrence of paroxysmal atrial fibrillation with thoracic vertebra hyperplasia.
Axial and coronal chest CT images show severe calcification that projected into the right anterior side of the thoracic vertebra and adhesion of spurs on the top and bottom vertebral borders and intervertebral joint in seven vertebrae (Fig. A). On the voltage map during catheter ablation, many local low voltage areas ranging from red to yellow can be observed (Fig. B). The area circled in white shows the region impacted by a vertebral spur near the pulmonary vein at the right of the posterior wall of the left atrium.

to osteoporosis onset. Furthermore, continuous, chronic mechanical irritation of fibrous connective tissue may cause hyperostotic changes. A typical disease associated with bone proliferation is DISH. Its pathology features activation of cartilage cells in soft tissue, and mainly ligament and tendon enthesis sites, leading to calcification and ossification [15]. The presence of both age-related intervertebral disc changes and DISH can cause cartilage cells to bulge, causing significant osteogenic changes in the anterior spinal cord. Although no clear mechanism of onset has been demonstrated, vitamin A metabolism disorders, calcium metabolism disorders, glucose metabolism disorders and hormone metabolism disorders are known to affect ligament ossification. DISH has been found to be related to obesity, impaired glucose tolerance and adult-onset type 2 diabetes. In fact, it has been reported that 13–50% of type 2 diabetes patients have DISH. The high prevalence of metabolic syndrome amongst DISH patients means that the prevalence of hypertension, diabetes and old cerebral infarction are also high [16, 17], and hospitalization due to paroxysmal atrial fibrillation also tends to be common [18].

It has been reported that in addition to metabolic disorders, insulin-like growth factor-1 (IGF-1) is also related to DISH onset [19, 20]. IGF, which is secreted by the liver in response to growth hormone stimulation, is a polypeptide that, like insulin, regulates induced response to mitosis. Low levels of IGF-1 are thought to be related to age-related changes of the coronary artery, coronary artery disease, stroke and cardiovascular mortality [21–25]. IGF-1 exhibits direct anti-apoptosis action on atrial muscle [26, 27], and atrial fibrillation patients have significantly lower levels of IGF-1 and insulin-like growth factor binding protein 3 (IGFBP-3) than non-atrial fibrillation patients [18]. These research results suggest that metabolism disorders and adjustment factors related to the diffuse hyperostosis process may have a common cascade with the onset mechanism for atrial fibrillation.

In the present study, we found that all cases with hyperostosis exhibited characteristic ossification projecting anteriorly into vertebrae. Physical displacement such as this may have raised BNP by forming low voltage in the neighboring left atrial posterior wall and inhibiting left atrial dilatation. However, because low voltage due to a spur at the left atrial site of impaction was not necessarily observed in all cases, there may be a common phylogenetic basis for the onset of both bone proliferation and atrial fibrillation.

CONCLUSION

Results suggested that thoracic vertebra hyperplasia could be a marker for relapse following PVI in patients with pAF.

LIMITATIONS

1. In this study, when osteolysis projecting onto the spine was observed in at least one site on the upper or lower border of a thoracic vertebral body, this was considered to indicate the presence of hyperostosis, as described the method section. Generally, a thoracic vertebra lesion is the most frequent occurrence as a spine pathology in the SAPHO syndrome, and the cervical

spine lesion is rare. It was classified into three types of corner lesion: non-specific spondylodiscitis type, osteosclerosis type, and paravertebral ossification type [28, 29]. However there is no standard criteria about the simple hyperplasia in the diagnostic imaging, and therefore steady and constant level of judgement is difficult even for the orthopedic surgeon.

2. In the present study, the small overall sample size made multivariate logistic analysis impossible. We were also unable to clarify the characteristics of hyperostosis patients in the relapse group with DISH and those without DISH. To demonstrate the utility of thoracic vertebra hyperplasia as a relapse factor in patients with paroxysmal atrial fibrillation following pulmonary vein isolation, further investigation is required in the future on a larger study sample.

DISCLOSURES

There is no disclosure in this study.

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