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Putative role of prosthetic dental implants in the development of cardiac sarcoidosis: A case-control study

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Abstract. Background: Etiopathogenesis of cardiac sarcoidosis is poorly understood. The objective of this study is to examine a possible role of previous dental procedures on the development of cardiac sarcoidosis (CS). **Methods:** Clinical details of 73 patients with CS from the Granulomatous Myocarditis Registry were extracted. Data regarding clinical presentation, comorbidities, baseline electrocardiogram, echocardiogram, and ^{18}fluorodeoxyglucose(FDG) PET-CT was extracted from the registry database. A comprehensive history of dental procedures for all patients was recorded. The two control groups comprised of 79 patients with idiopathic ventricular tachycardia and/or complete heart block (with similar clinical presentation) and 145 healthy age and sex matched patients, respectively. **Results:** Dental evaluation revealed that patients with CS had undergone a previous prosthetic dental implant(PI) (OR 12.4, 95% CI 4.0-38.1, p<0.001) or root canal treatment (RCT) (OR 2.43, 95% CI 1.12-5.26, p=0.025) more often than the healthy controls. The patients with CS and previous dental procedures had higher^{18}FDG uptake in the LV myocardium (SUV max 8.6±3.3vs.5.5 ±1.8 (mean±SD), p<0.001) and mediastinal lymph nodes (9.3±4.6vs.5.4±1.7 (mean±SD), p<0.001) as compared to patients who did not undergo a dental procedure. The subset of CS patients with a previous PI or RCT had higher uptake levels in the myocardium (max SUV 9.4±3.1vs.6.7±2.0, p=0.011, number of abnormal LV Segments 10.3±3.1vs.6.5±2.8(mean±SD), p=0.008) and mediastinal lymph nodes(max SUV 10.5±4.8vs. 7.2±1.8,p=0.002) compared to those who underwent crowning or extraction. In addition, CS was diagnosed after a shorter latency period (47.3±21.0vs.81.6±25.3 months (mean±SD), p<0.001) following PI and RCT compared to other dental procedures. **Conclusions**: We observed a significant association between PI and RCT and the occurrence of CS. This group of patients also appear to have a more severe form of the disease.

Introduction

Sarcoidosis is a granulomatous inflammatory disease triggered by a number of different antigens (1). Cardiac involvement may be part of a generalized systemic sarcoidosis or it could be isolated to heart and mediastinal nodes. Exposure to environmental antigens in a genetically susceptible host is considered to trigger granulomatous inflammation in sarcoidosis. Case control studies have demonstrated that inhaled agents from the environment may be involved in the pathogenesis of pulmonary sarcoidosis (2-4). Increased risk of sarcoidosis among those with a specific occupational exposure history has been observed, supporting this notion (5,6). While pulmonary sarcoidosis may be related to an inhaled antigen, CS (in the absence of pulmonary involvement) could potentially be related to an antigen entering the blood stream directly.

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Use of various biomaterials has increased among prosthetic dental implantations. Large number of such implants are performed every year (7). Various metals, alloys, and inert filling materials used in dental procedures have been shown to incite a chronic inflammatory tissue response.[8]Furthermore, occupational exposure to a number of metals that are commonly present in prosthetic dental implants, including zirconium and titanium, have been shown to result in granulomatous inflammation resembling sarcoidosis (8). The aim of this study was to investigate a possible association between cardiac sarcoidosis and previous dental procedures.

Methods

Patient Identification and Eligibility

We retrospectively analyzed the data of 73 consecutive patients diagnosed with CS enrolled in the Granulomatous Myocarditis Registry with the approval of the CARE Foundation Institutional Ethics Committee and Review Board (ID 3-01072012) and written informed consent was obtained from all patients. All patients with granulomatous myocarditis (including CS) were enrolled in this registry from 2010. The methods of case identification, diagnosis, data collection, and management of the patients in this registry have been described by our group previously (9). In brief, the diagnosis of CS was made with a combination of ^{18}fluorodeoxy glucose positron emission tomography scan (^{18}FDG-PET CT scan) findings consistent with CS and histological evidence of extra-cardiac sarcoidosis. These criteria are in accordance with the recent guidelines for diagnosis of extra cardiac CS (10). As a part of the registry, weekly multidisciplinary (cardiologist, rheumatologist, pulmonologist) clinical meetings are used to diagnose, initiate, and optimize treatment of patients with CS. Patient preparation for the ^{18}FDG-PET CT scan consisted of commencing a high fat, low carbohydrate diet 48 hours before the study followed by fasting for 8-12 hours (11). In this study, we included consecutive patients diagnosed with CS from January 2014. Other causes of granulomatous myocarditis were excluded from this study cohort.

Two different control groups were used in this study. Control group 1 consisted of 145 age and sex frequency matched healthy subjects without structural heart disease. These healthy subjects consisted of individuals undergoing annual health (medical and dental) check-ups in the same tertiary care hospital. Control group 2 was made up of 79 patients in whom CS was suspected and underwent evaluation during the same time period that the cases were enrolled. These patients presented with either idiopathic ventricular tachycardia (VT) or complete heart block and did not have any structural heart disease or myocardial uptake detectable on cardiac magnetic resonance and ^{18}FDG-PET CT, respectively. All study procedures were in accordance with the Declaration of Helsinki.

Data Extraction

Clinical data regarding symptoms, comorbidities, baseline electrocardiogram, echocardiogram, and ^{18}FDG PET-CT were extracted from the registry database. The following ECG parameters were measured: RR interval, PR interval, QRS duration, and the presence of bundle branch block. With regards to echocardiography, baseline left ventricular ejection fraction, presence of regional wall motion abnormalities, and pulmonary artery pressure were included.

Myocardial and mediastinal uptake was studied by ^{18}FDG PET-CT images analyzed in standard short-axis, horizontal long-axis, and vertical long axis views using the standard American Society of Nuclear Cardiology (ASNC) 17 segment model of the LV (12). The number of abnormal segments with increased FDG uptake was recorded for each patient. Visual analysis was used to identify the presence or absence of RV uptake on trans-axial images. Furthermore, FDG activity was also quantified by recording the maximum standardized uptake value (SUV) in the LV myocardium and mediastinal lymph node. Uptake index (UI) was defined as the product of the maximum LV myocardial uptake (SUV) and the number of LV segments with abnormal uptake.

Utilizing patient interviews and/or review of hospital medical records, a comprehensive history of dental procedures for all patients in the study and control groups was obtained. Echocardiography, ^{18}FDG PET-CT and magnetic resonance imaging were used to exclude structural heart disease in the controls. All patients and healthy controls were examined by a qualified dentist (AS). Previous interventions including root canal treatment(RCT), prosthetic dental

Table 1. Baseline Characteristics of controls and patients with cardiac sarcoidosis (cases).

	Control Group 1* (N=145)	Control Group 2** (N=79)	Cases (N=73)	P-value
Age	43.1±12.2	42.7±13.9	45.3±13.1	0.476
Male Sex	93(64.1%)	49(62.0%)	50(68.5%)	0.698
Comorbidities				
Systemic Hypertension	43(29.7%)	24(30.4%)	28(38.4%)	0.406
Diabetes Mellitus	39(27.0%)	22 (27.8%)	17(23.3%)	0.794
History of previous dental procedure	44(30.3%)	16(20.3%)	38(52.1%)	<0.001
Dental Implant	4(2.8%)	5(6.3%)	19(26%)	<0.001
Root Canal Treatment	15(10.3%)	7(8.9%)	16(21.9%)	0.025
Crowning	20(13.8%)	11(13.9%)	9(12.3%)	0.818
Extraction	15(10.3%)	8(10.1%)	4(5.5%)	0.468
Multiple Procedures ≥ 3	7(4.8%)	6(7.6%)	13(17.8%)	0.005

**Control Group 1: Healthy age and sex matched controls. **Control Group 2: Patients with idiopathic ventricular tachycardia and AV block evaluated and found to not have cardiac sarcoidosis. Data are number of patients (%) or mean (SD).*

implantation(PI) surgery, dental crown cementation surgery and tooth extraction were included. Patients who underwent only crown cementation without root canal treatment were included in the crowning group. The interval between the first dental procedure and the diagnosis of cardiac sarcoidosis was documented.

Statistical Analysis

The Shapiro-Wilk test was performed to find whether a parameter is distributed normally. Data are presented as mean ± standard deviation and as proportions for continuous and categorical parameters, respectively. Continuous variables were compared using the unpaired student t-test or U Mann-Whitney test, as appropriate. The Fisher's exact test was used to compare categorical variables. To investigate group differences between controls and cases, variables were compared between groups using analysis of variance (ANOVA). To evaluate the association between dental procedures and CS, an odds ratio (OR) and 95% confidence interval were calculated. For all analysis, a two tailed P value < 0.05 was used to define statistical significance.

Results

Baseline Patient Characteristics

Baseline characteristics of the cases and controls are described in Table 1. The majority of patient data of cases was extracted through patient interviews (89%) and the remaining was obtained through review of records. All data of controls was extracted through patient interviews. Among control group 2, 71 patients (89.9%) had idiopathic VT and 8 patients (10.1%) had idiopathic complete heart block. Patients with CS had undergone dental procedures more often compared to both control groups. Patients with CS had a higher number of prosthetic dental implants and root canal treatments, compared to controls (Figure 1). The association of CS with previous dental procedures in cases and both control groups is depicted in Table 2.

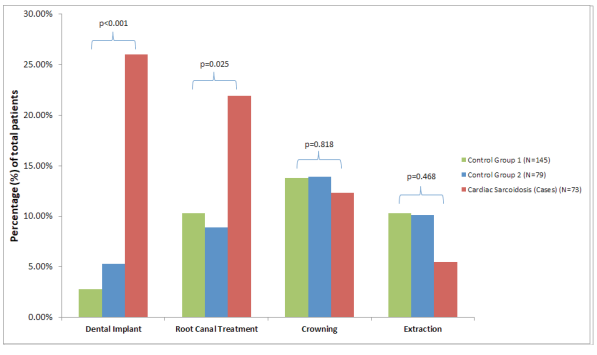

Figure 1. Dental procedures in cases and controls. Patients with CS had a higher number of prosthetic implants and root canal treatments compared to patients in control group 1 and 2.

Table 2: Association of CS with exposure to previous dental procedures in cases and matched controls

Exposure	Control Group 1 (N=145)	Control Group 2 (N=79)	Cases (N=73)	OR (95% CI) (Control Group 1 vs. Cases)	OR (95% CI) (Control Group 2 vs. Cases)
Prosthetic Dental Implant	4	5	19	12.4 (4.03–38.12)	5.21 (1.83-14.82)
Root Canal Treatment	15	7	16	2.43 (1.12-5.26)	2.89 (1.11-7.49)
Crowning	20	11	9	0.88 (0.38-2.04)	0.87 (0.34-2.24)
Extraction	15	8	4	0.50 (0.16–1.57)	0.30 (0.15–1.79)

OR-Odds Ratio.CI-Confidence Interval. Refer to Table 1 for other abbreviations.

Dental procedures in CS patients

Among the CS group, VT occurred in 66 patients (90.4%) and the remaining 7 patients (9.6%) had isolated AV block. There were no differences between CS patients with and without history of previous dental procedures with regards to clinical presentation, baseline electrocardiogram, and echocardiographic measurements (Table 3). However, quantitative analysis revealed that CS patients with previous dental implants had a higher baseline maximum SUV of FDG in both the LV myocardium and mediastinal lymph nodes. In addition, a greater number of LV myocardial segments were affected on PET evaluation in patients with previous dental procedures.

Table 3. Baseline Characteristics of CS patients with and without prior dental procedures

	Patients without prior dental procedure (N=35)	**Patients with prior dental procedure (N=38)**	**P-value**
Age	43.1±13.5	46.4±12.4	0.275
Male Sex	24(68.6%)	26(68.4%)	0.989
Comorbidities			
Systemic Hypertension	15(42.9%)	13(34.2%)	0.448
Diabetes Mellitus	10(28.6%)	7(18.4%)	0.305
Clinical Presentation of CS			
AV Block	6(17.1%)	4(10.5%)	0.411
Heart Failure	17(48.6%)	18(47.4%)	0.918
Ventricular Arrhythmias	18(51.4%)	18(47.4%)	0.729
Other organ system involvement			
Lymph Nodes	35 (100%)	38 (100%)	NA
Pulmonary	2 (5.7%)	3 (7.9%)	0.712
CNS	2 (5.7%)	1 (2.6%)	0.501
Other	1 (2.9%)	2 (5.3%)	0.610
Baseline ECG			
PR Interval	161.9±24.1	156.2±33.0	0.399
QRS width	103.6±21.6	105.0±19.8	0.769
Bundle Branch Blocks	8 (22.9%)	14(36.8%)	0.199
Atrial Fibrillation	5(14.3%)	4(10.8%)	0.656
Baseline 2D Echocardiogram			
LV Function (EF %)	44.3±13.5	45.0±14.9	0.838
RWMA	14(40%)	14(36.8%)	0.782

	Patients without prior dental procedure (N=35)	Patients with prior dental procedure (N=38)	P-value
Pulmonary Artery Pressure	28.0±11.8	32.9±13.3	0.103
Baseline ^{18}FDG -PET Scan			
Maximum uptake in LV myocardium (SUV)	5.5 ± 2.3	8.6 ± 3.3	<0.001
Number of LV segments involved	5.4 ± 2.1	9.1 ± 3.8	<0.001
RV Uptake	1(2.9%)	4(10.5%)	0.351
Maximum uptake in lymph nodes (SUV)	5.4 ± 1.7	9.3± 4.6	<0.001

Data are number of patients (%) or mean (SD). RWMA-Regional wall motion abnormalities. LV-Left Ventricle. RV-Right Ventricle. SUV-Standardized uptake value.

FDG PET and dental procedures

Patients who received a prior PI or RCT had significantly higher maximum SUV in the LV myocardium, mediastinal lymph nodes, and greater number of abnormal LV segments compared to patients who did not undergo a dental procedure (Figure 2A-2C). There was no difference in FDG uptake or distribution among CS patients with a dental extraction or crowning compared to those without a dental history. Patients with a previous PI or RCT had higher uptake levels in the myocardium (Max SUV 9.4 ± 3.1 vs. 6.2 ± 1.8, p=0.011, number of abnormal LV Segments 10.3 + 3.1 vs. 5.5 ± 1.6, p=0.008) and mediastinal lymph nodes (Max SUV 10.5 ± 4.8 vs. 6.5± 1.8, p=0.002) compared to patients who had a previous history of only crowning or extraction. When comparing patients who underwent only a PI to those who underwent only a RCT, there was no difference with regards to uptake in the myocardium (Max SUV 7.2 ± 2.7 vs. 9.0 ± 2.2, p=0.077, number of abnormal LV segments 9.5 ± 4.4 vs. 10.8 ± 3.2, p=0.231) or mediastinal lymph nodes (Max SUV 9.7 ± 6.1 vs. 9.3 ± 4.7, p=0.411).

Latency period after dental procedures

Among all patients with CS who had a previous dental procedure, the average duration between the procedure and the diagnosis of cardiac sarcoidosis was 56.3 + 24.8 months (Range 16 – 104 months). Patients who had undergone a PI or RCT had a significantly shorter latency between the dental procedure to CS diagnosis compared to patients who underwent crowning or extraction (47.3 + 21.0 vs. 81.6 + 25.3 months, p<0.001). (Figure 3) In addition,

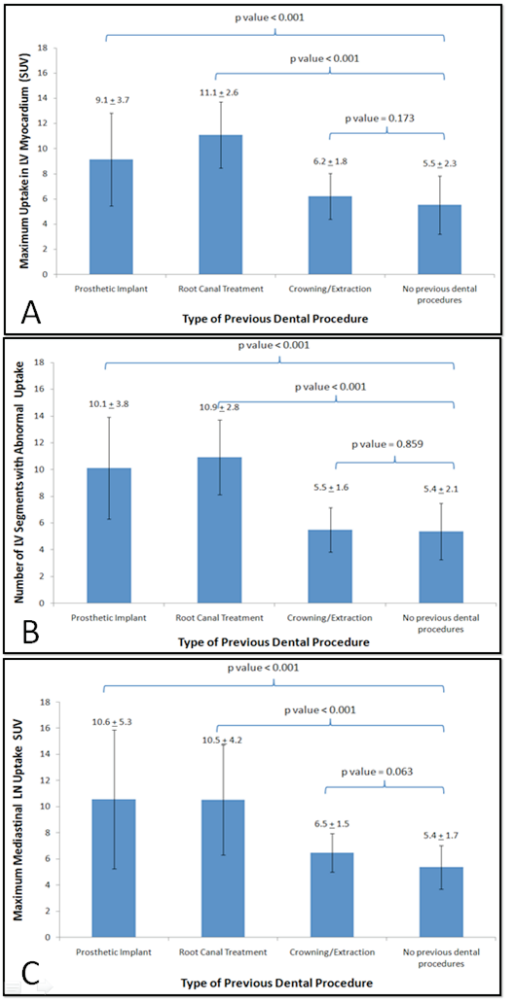

Figure 2. Findings on ^{18}FDG PET-CT stratified by type of dental procedure. Findings on ^{18}FDG PET-CT in patients with CS stratified by type of procedure according to maximum uptake in the LV myocardium (SUV) (Panel A), number of LV segments with abnormal uptake (Panel B), and maximum mediastinal lymph node (LN) Uptake (SUV) (Panel C).

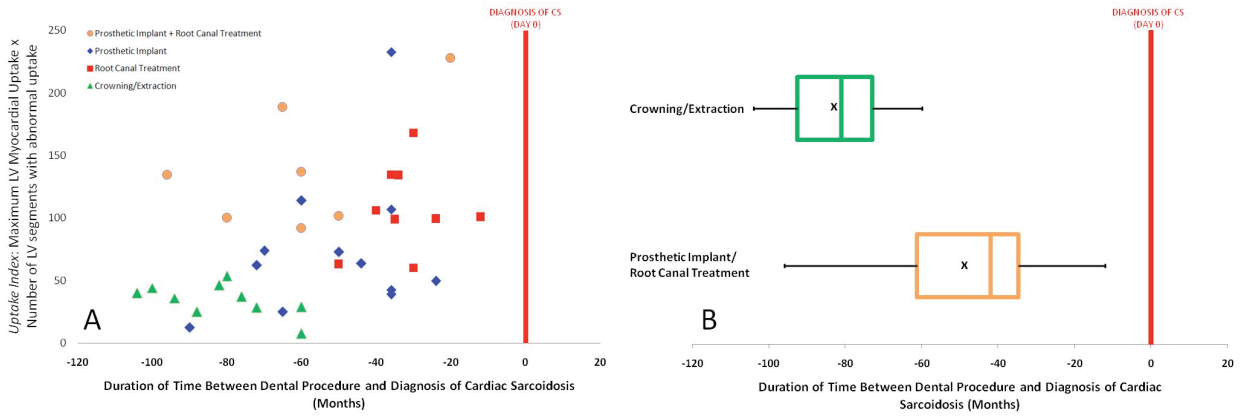

Figure 3. Temporal and dose-response relationship of dental procedures with cardiac sarcoidosis. Scatter plots (A) and box-and whisker plots (B) demonstrating the temporal (duration between dental procedure and diagnosis of CS) and dose-response relationship (uptake index) of types of dental procedure with occurrence of CS. In the box-and-whisker plots, the middle line represents the median; the right and left sides of the box represent the first and third quartiles, respectively; right and left whiskers represent the highest and lowest data points and the "x" represents the mean value.

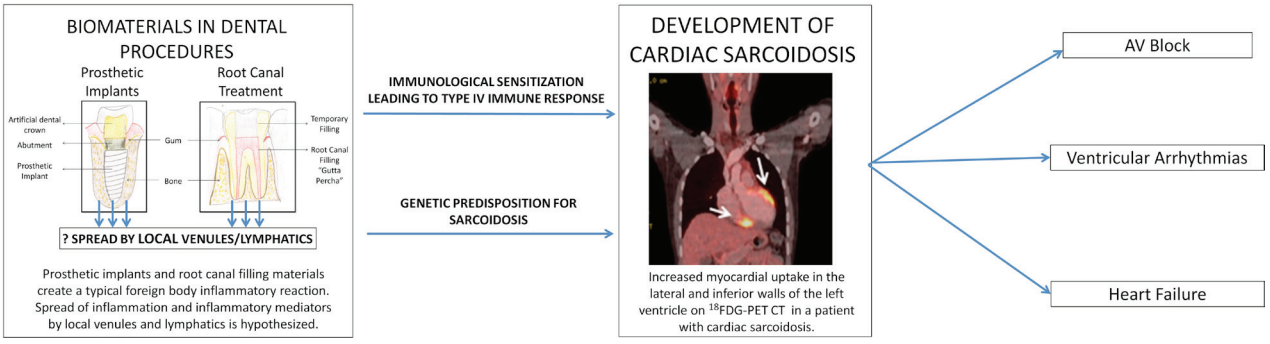

Figure 4. Proposed association between dental procedures and cardiac sarcoidosis. Exposure to prosthetic dental implants and root canal treatments are associated with an increased occurrence of cardiac sarcoidosis. A foreign body induced chronic inflammatory response may lead to immunological sensitization in a genetically prone individual

patients with PI and/or RCT also had a higher uptake index (101.5± 55.0 vs. 34.7 ± 13.0, p<0.001) compared to patients with crowning or extraction. The association between prior dental procedures (PI and RCT) and CS is summarized in Figure 4.

Discussion

In this case-control study we observed an association between prior dental interventions (PI and RCT) and occurrence of CS. This group of patients with CS, (PI and RCT) had a more severe form of disease compared to patients without a history of dental procedures.

In modern dentistry, different biomaterials are utilized for achieving optimal functional and aesthetic outcomes. Pure titanium, zirconium, and titanium alloys have been preferred due to their biocompatibility and mechanical properties, respectively (13). Several studies have suggested that occupational and environmental exposure to a number of metals including beryllium, zirconium, and titanium can result in granulomatous inflammation resembling sarcoidosis (14-17). However in contrast to environmental agents that often target the lungs and skin, endosseous dental implants undergo a process of osseointegration in which they create a local inflammatory tissue response (18). It is possible that

crowns, although made of similar biomaterials, are exposed to only the buccal and gingival mucosa and not to blood stream making them less likely to cause cardiac disease. Dental implants are more likely to be exposed to blood (through sublingual and submandibular venules and lymphatics) resulting in systemic side effects (19,20).

The filling material used in RC treatment is composed of about 20% gutta-percha, 60-75% zinc oxide and varying amounts of metal sulphates for radio-opacity (21). Although considered to be biocompatible and safe, the particulate materials and leaching zinc oxide within the gutta-percha has been reported to induce a foreign body chronic inflammatory reaction characterized by macrophages and giant multinucleated cells (22,23). Immunological sensitization to root canal fillings was seen in patients with systemic disease and was attributed to a type IV immune response involving interferon gamma and interleukin-10 (24). The very same mediators are involved in the granulomatous inflammation of sarcoidosis. In addition, the increased exposure to various occupational dusts and chemicals, including beryllium, during dental procedures has been associated with granulomatous inflammation (25,26).

Sarcoidosis is thought to occur in patients with genetic susceptibility to the disease who are exposed to inciting antigens– the so called "two-hit" hypothesis (27). The specific response of an individual to an environmental trigger, in this case a prosthetic implant or root canal treatment, is influenced not only by the local tissue inflammatory reaction but also by the underlying genetic and immunological predisposition.

We believe that this study fulfills the Bradford Hill criteria of strength of association, temporality, plausibility and coherence to attribute causation in a study (28,29).

The main limitation of this study is its retrospective nature. History of dental procedures in this study may introduce a recall bias and overestimation of the association between these procedures and cardiac sarcoidosis. As none of the patients refused participation in the study, participation bias was minimal in this study. In addition, there may be currently undefined confounding factors that affect the prevalence of both dental procedures and CS. Due to multiple different types of dental biomaterials used in these patients and complexity in quantifying these biomaterials after the dental procedure, it is difficult to understand the specificity of exposure and the presence of a biological gradient. The impact of recall bias on study results was minimized by dental examination of all patients. Although there are limitations to using the 17-segment model for quantifying ^{18}FDG PET uptake, we incorporated multiple parameters (maximum SUV, number of abnormal segments, uptake index) in this study. Most importantly, we need large prospective studies to not only show a consistent level of causation but also to institute preventive action.

Conclusions

In this case control study we observed an association of prosthetic dental implants and root canal treatment with the occurrence of cardiac sarcoidosis. Although we have observed a temporal association and a dose response between PI/RCT and CS, further studies are required to understand the mechanism and establish causal relationship to CS.

Abbreviations: CS: cardiac Sarcoidosis; 18FDG-PET CT: 18Fluorodeoxy glucose positron emission tomography; ASNC: American Society of Nuclear Cardiology; SUV: standardized uptake value (SUV); OR: odds ratio (OR); UI: Uptake Index; PI: prosthetic dental implants; RCT: root canal treatment; VT: ventricular tachycardia

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Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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