Clinical analysis of the effect of anti-allergy treatment on pocket-related complications following pacemaker implantation

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Abstract. A total number of 339 patients who received a pacemaker implantation between June 2012 and June 2014 at Tongji Hospital of Tongji Medical College (Wuhan, China) were investigated in the present study. The aims of the present study were to explore the risk factors of pocket hematoma following pacemaker implantation, and to analyze the effect of anti-allergy treatment on pocket-related complications following pacemaker implantation. Predictors of hematoma occurrence were determined and analyzed via a Chi-square test. Patients suffering from pocket hematoma, which were indicated to be partially caused by an allergic reaction to the pacemaker component, were distinguished by routine blood parameters. Furthermore, the pacemaker component was distinguished by histopathological examinations in one patient. Promethazine (25 mg/day) was used to treat allergic patients. The results demonstrated that in patients with a history of allergies, the rate of pocket hematoma was significantly higher when compared with patients without a history of allergies (22.00 vs. 7.61%; P=0.027). A significantly increased incidence of hematoma was indicated in patients with a lower body mass index when compared with patients of normal weight (15.79 vs. 7.38%; P=0.042). Furthermore, implantation of larger-sized devices, such as an implantable cardioverter-defibrillator and cardiac resynchronization therapy, were significantly predictive of hematoma development (29.63 vs. 8.01%; P=0.015). Patients with diabetes were also identified to exhibit a significantly high incidence of hematoma (22.22 vs. 8.25%; P=0.023). Promethazine administration significantly decreased the incidence of re-operating (P=0.017) and the duration of hospital stay (P=0.038) in patients whose pocket hematoma was caused by an allergy. In conclusion, promethazine may be a beneficial agent to treat pocket hematoma caused by allergic reactions following pacemaker surgery.

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Introduction

Permanent pacemaker implantation via implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) has been commonly used in the treatment of bradyarrhythmia, heart failure and the prevention of sudden death; however, the rate of pacemaker implantation complications has increased by 3 to 4% (1,2). Among some of the most common complications with an incidence of 0.2 to 0.6%, pocket hematomas have been demonstrated to be particularly harmful. These complications are associated with prolonged hospitalization, increased hospital charges, slow wound healing, typically result in re-operation and may cause surgery failure (3,4). Furthermore, hematoma may increase the risk of infection and cause endocarditis (3-5). Therefore, whether pocket hematoma may be prevented and treated would affect the success of pacemaker surgery.

Promethazine acts as a histamine (H1) receptor antagonist, muscarinic antagonist and dopamine antagonist (6) and is suitable for treating allergic conditions (7). Additionally, promethazine is commonly used for treating allergies caused by the injection of traditional Chinese medicine products (7), such as Salvia miltiorrhiza.

The present study determined the predictors of pocket hematoma by analyzing the data of patients who were previously subjected to pacemaker surgery via univariate comparison, and subsequently investigated the effectiveness of the anti-allergy drugs for treating pocket hematoma via immunohistochemical examination.

Materials and methods

Study population. A total of 339 patients (184 men and 155 women), who were previously subjected to permanent pacemaker implantation between June 2012 and June 2014,

were investigated in the present study. Additionally, a total of 100 healthy individuals (50 men and 50 women) were also involved in the present study as the control/normal group. The present study was approved by the Ethics Committee of Huazhong University of Science and Technology (Wuhan, China). All patients provided their informed written consent and approved the publication of the study.

Inclusion criteria included the following: Third or second degree type 2 auriculoventricular block; patients with sick sinus syndrome, mean heart rate ≤40 bpm with significant clinical symptoms (amaurosis and syncope); signed the informed consent; battery depletion and atrial fibrillation with 3 sec RR interval and significant clinical symptoms, or 5 sec RR interval. Exclusion criteria included the following: Patients with severe trauma; patients who received antibiotics within 72 h prior to implantation; patients who received dialysis treatment; patients who had hemorrhagic diseases; patients who presented with a tumor; and patients who received immunodepressants/hormones.

Clinical data analysis. Clinical characteristics and the follow-up data of the patients were investigated in the present study via univariate comparison. The age, gender, body mass index (BMI), presence of cardiovascular disease, history of diabetes, type of the pacemaker fitted, left ventricular function, use of anti-platelet/anti-coagulant agents or not, number of surgeries, allergy history and whether pocket hematoma was indicated or not, was evaluated and analyzed.

Immunohistochemical analysis. Samples which were cut from the pocket during surgery were collected for immunohistochemical examination. Samples of blood were collected from the patients and the control/normal individuals. Samples were promptly fixed with 10% formalin at the room temperature and subjected to dehydration and paraffin embedding. Paraffin sections were cut into 3-μm thick sections. Deparaffinization, rehydration and deactivation of endogenous enzymes in the paraffin sections were performed for immunohistochemical analysis. Briefly, slides in 0.01 M sodium citrate buffer (Sigma-Aldrich; Merck Millipore, Darmstadt, Germany; pH 6.0) were incubated at 99-100˚C for 20 min. Slides were subsequently removed from the heat and maintained in cool buffer at room temperature for 20 min before being rinsed in Tris-buffered saline with 0.1% Tween-20 (Aviva Systems Biology Corp., San Diego, CA, USA) at room temperature for 1 min. Following incubation overnight at 4˚C with goat anti-human CD3 polyclonal antibody (sc-1128; 1:2,000), mouse anti-human CD43 monoclonal antibody (sc-70681; 1:3,000), mouse anti-human CD34 monoclonal antibody (sc-65261; 1:3,000; all Santa Cruz Biotech., Santa Cruz, CA, USA) and rabbit anti-human CD99 monoclonal antibody (ab10829; 1:2,000; Abcam Biotech., Cambridge, MA, USA), separately, the samples were exposed to horseradish peroxidase-conjugated anti-rabbit IgG secondary antibody (1:5,000; cat. no. W4011; Promega Corp., Madison, WI, USA). Subsequently, 3,3'-diaminobenzidine (Cell Signaling Technology, Inc., Danvers, MA, USA) was used to visualize the expression of proteins stained with hematoxylin and eosin. All samples were checked with light microscope.

Therapy. Histopathological examination, cytological examination and bacterial culture were used to characterize pocket hematomas. Samples, which include the routine blood parameters, were collected immediately after surgery. Promethazine (Shanghai Hefeng Pharmaceutical Co., Ltd; 25 mg/day) was administered within 48 h of surgery to 9/11 patients who agreed to receive intramuscular injections to evaluate the efficacy of anti-allergy treatment on pocket hematoma. Samples that were obtained during surgery were placed in 10% neutral formalin solution for 24-h fixation at room temperature, following dehydration in an alcohol series. Subsequently, the pocket tissues were embedded in paraffin, cut into 4-μm-thick slices, dewaxed and hydrated prior to staining with hematoxylin for 5 min. Following staining, the slices were hydrated for 10 min, eosin-stained for 2 min, dehydrated, hyalinized and turpentine-mounted before the samples were observed under a light microscope. Pocket hematoma samples (5-8 ml), which were aseptically aspirated, were collected in falcon tubes and sent for cytological examination and bacterial culture. As a quality control measure for Luria Broth culture, which was produced by Tongji college, sterility and performance testing was done. Sterility testing was performed by extracting 3-5% of each batch and incubating at 35˚C for 2 days.

Statistical analysis. Data are expressed as the mean ± standard deviation. Data were analyzed using a Student's t-test with SPSS version 19 statistical software (IBM SPSS, Armonk, NY, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics and incidence of pocket hematoma. A total of 184 men and 155 women, with an average age of 62.88±14.36 years, were investigated. The characteristics of the study participants are presented in Table I. The incidence of pocket hematoma in the present study was indicated to be 9.73%. The risk factors of pocket hematoma complicating permanent pacemaker implantation included: Large-sized pacemaker; history of diabetes; allergies; and low BMI. Pocket effusion or hematoma resulted in prolonged hospital stays in 27 patients (81.82%) and led to re-operations in 10 patients (30.30%).

Effect of age, gender and BMI on pocket effusion or hematoma. The present findings indicated that pocket effusion or hematoma was not associated with the patient's age or gender; however, BMI was indicated to influence pocket effusion or hematoma. Previous results have that patients who were >75 years old were more likely to have suffered from pocket hematoma (3). In the present study, the age of patients was not related to pocket effusion or hematoma, which may be due to the low implantation rate of elderly patients (Table II).

Medical history was indicated to have had an enormous impact on the incidence of pocket effusion or hematoma, particularly any medical history of diabetes. Pocket effusion or hematoma was indicated to be related to a medical history of allergies. In the present study, no association was identified between pocket effusion or hematoma and low ejection

Table I. Patient characteristics.

Characteristic	Value
Number of patients	339
Age	62.88±14.36
Number of women	155
Number of men	184
Reduced LV function[a]	46
Anticoagulant/antiplatelet therapy	45
First surgery	291
Cardiovascular disease	110
Diabetes	36
Allergy	50
Low BMI[b]	95
Large pacemaker[c]	27
Incidence of pocket hematoma (%)	9.73

[a]Ejection fraction <50%; [b]BMI<18.5 kg/m^2; [c]including implantable cardioverter defibrillator, cardiac resynchronization therapy and cardiac resynchronization therapy with defibrillator. LV, left ventricular, BMI, body mass index.

Table II. Effect of age, gender and BMI on pocket effusion or hematoma.

Risk factors	Number of patients	Incidence of effusion or hematoma (%)	P-value
Age			>0.05
<75 years	267	10.49	
≥75 years	72	38.76	
Gender			>0.05
Male	184	12.50	
Female	155	6.45	
BMI			<0.05
Low BMI[a]	95	15.79	
Normal BMI	244	7.38	

[a]BMI<18.5 kg/m^2. P-values represent the differences in the incidence of effusion or hematoma (%) between the two sub-groups within each of the three risk factors. BMI, body mass index.

fraction value or cardiovascular disease, including coronary heart disease and atherosclerosis (Table III).

It was hypothesized that patients who were subjected to more than one surgery may suffer from pocket effusion or hematoma more easily. However, the number of surgeries was identified to not be related to the incidence of pocket effusion or hematoma. Notably, the size of the pacemaker component was demonstrated to elicit a significant effect on the incidence of pocket effusion or hematoma. Large-sized pacemakers, such as ICD, CRT and CRT with the defibrillation function

Table III. Effect of past medical history on pocket effusion or hematoma.

Risk factors	Number of Patients	Incidence of effusion or hematoma (%)	P-value
History of cardiovascular disease			0.054
Yes	110	7.27	
No	229	10.92	
History of diabetes			0.023
Yes	36	22.22	
No	303	8.25	
History of allergic reaction			0.027
Yes	50	22.00	
No	289	7.61	
Left ventricular EF			0.069
Low EF value[a]	46	10.87	
Normal EF	293	9.56	

[a]EF<50%. P-values represent the differences in the incidence of effusion or hematoma (%) between the two sub-groups of each of the four respective risk factors. EF, ejection fraction.

Table IV. Effect of the number of operations and pacemaker size on incidence of pocket effusion or hematoma.

Risk factors	Number of patients	Incidence of hematoma (%)	P-value
Surgical history			>0.05
First	291	9.62	
Subsequent	48	10.42	
Type of the pacemaker			<0.05
Large pacemaker[a]	27	29.63	
Normal pacemaker	312	8.01	

[a]Including implantable cardioverter defibrillator, cardiac resynchronization therapy and cardiac resynchronization therapy with defibrillator. P-values represent the differences of incidence of hematoma (%) between the two sub-groups within each of the two respective risk factors.

(CRT-D), significantly increased the incidence of pocket effusion or hematoma (P<0.05; Table IV).

Efficacy of anti-allergy treatment. If no complications arose, patients with pacemaker implantations remained in hospital

Table V. Effect of allergy on the incidence of pocket effusion or hematoma.

Variable	Number of reoperations	Hospital stays following implantation (days)	P-value
Allergy	6	35.17±6.04	0.0001
Other risk factors	4	12.42±5.30	

Table VI. Blood routine parameters analysis of patients with allergic pocket effusion or hematoma.

Variable	Number of patients	Eosinophil (%)	Eosinophil	P-value
Allergy	11	8.47±9.45	0.46±0.30	0.023
Other risk factors	22	3.28±5.24	0.21±0.34	

Other risk factors included cardiovascular disease, diabetes and left ventricular ejection fraction in the present study. Data are expressed as the mean ± standard deviation. P=0.023 represents the eosinophil (%) in the allergy group compared to the other risk factors.

Table VII. Effect of anti-allergic treatment on the incidence of pocket effusion and the duration of hospital stay.

Treat with promethazine	Number of patients	Incidence of reoperation (%)	Hospital stay after treatment (days)
No	7	71.43	16.71±7.57
Yes	9	11.11	8.10±5.86
P-value	16	P=0.017	P=0.038

P-value represents the differences in the incidence of reoperations or the hospital stays between the two groups indicated.

Table VIII. Effect of anti-platelet therapy on the incidence of pocket effusion or hematoma.

Anti-platelet therapy	Number of patients	Incidence of pocket effusion or hematoma (%)	P-value
No	20	70.2	0.084
Yes	45	68.4	

P-value represents the difference in the incidence of pocket effusion or hematoma between the anti-platelet therapy and no anti-platelet therapy groups.

for 7 to 8 days. The present findings indicated that pocket effusion or hematoma may cause prolonged hospital stays or even re-operation. Compared with other risk factors, such as cardiovascular disease, diabetes and left ventricular ejection fraction, allergic reactions to pacemakers was a relatively uncommon cause of pocket effusion or hematoma. However, allergic reactions to pacemakers were indicated to be more harmful and were able to significantly increase the period of hospital stay (P<0.05; Table V).

A case of an allergic patient who suffered from pocket effusion or hematoma. A 64-year-old female patient with a history of recurrent syncope for >1 month was examined. Following a diagnosis of third degree atrioventricular block by a local hospital, the patient was transferred to Tongji Hospital of Tongji Medical College (Wuhan, China). Subsequently, permanent pacemaker implantation was performed and the patient was transferred to a local hospital for recovery. The patient was subsequently transferred to Tongji Hospital of Tongji Medical College (Wuhan, China) after suffering with pocket hematoma. Pocket debridement surgery and temporary pacemaker implantation were performed following prolonged anti-infection treatment with 0.4 g/day levofloxacin (Yangtze River Pharmaceutical Group Co., Ltd., Taizhou, China) administered by intravenous drip. Histopathological examination of hematoxylin and eosin-stained tissues in the pocket revealed the proliferation of granulation tissue containing multinucleated giant cells (Fig. 1). The pocket hematoma was identified again following a permanent pacemaker implantation. A total volume of 5 ml of the bloody fluid in the pocket was examined by histopathological examination, cytological examination and bacterial culture. Only lymphocytes and a limited number of tissue cells were identified and no bacteria were present (Fig. 2). After considering the possibility that the patient experienced an allergic reaction, 25 mg/day of promethazine was intramuscularly injected over the course of 6 days. On October 18, 2012, the pocket hematoma was no longer apparent following 6 days of promethazine injection. Findings from this patient encouraged the examination of more pocket tissues. Histopathological examinations of pocket hematoma samples suggested that some of the pocket hematoma may have been caused by allergic reactions to the pacemaker (Fig. 3).

Routine blood parameters were also analyzed. A total of 11 patients were diagnosed with allergic pocket hematoma (Table VI) and 9 of these patients with allergic pocket hematoma were treated with intramuscular promethazine injection at a dose of 25 mg/day. The incidence of re-operations and the period of hospital stay following promethazine treatment were significantly decreased (P=0.017 and 0.038, respectively; Table VII).

Furthermore, 45 patients received anti-platelet therapy to observe the effects on the incidence of pocket effusion or hematoma. The results indicated that the anti-platelet therapy did not affect the incidence of pocket hematoma (Table VIII).

Discussion

Pocket effusion or hematoma has been indicated as a frequent early complication following pacemaker surgery, accounting

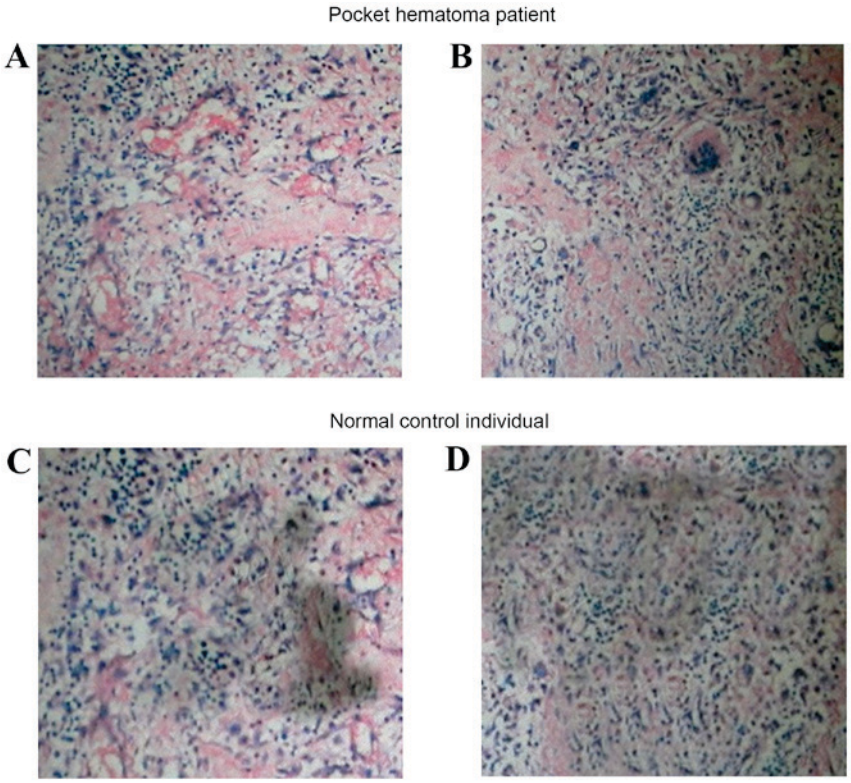

Figure 1. Granulation tissue proliferation was developed and multinucleated giant cells were identified in the pocket tissues of (A and B) a patient with pocket effusion or hematoma. However, this was not indicated in the tissues of (C and D) a normal individual. (A) Magnification, x200; (B) magnification, x400; (C) magnification, x200; and (D) magnification, x400.

for 14 to 17% of early re-operations (8). Due to its harmful effects, a previous study investigated the risk factors of pocket effusion or hematoma following pacemaker surgery (9). In the present study, various factors had been indicated to be associated with the increased risk of effusion or hematoma development. In particular, a medical history of allergies was revealed to be one of the most important risk factors, which has not been acknowledged until now. The present findings suggested that pocket effusion or hematoma caused by an allergic reaction was more serious and harmful when compared with pocket effusion or hematoma caused by other risk factors. Furthermore, previous studies have indicated that no effective treatment for pocket hematoma has been discovered (2-5).

A variety of factors may cause pocket effusion or hematoma, including the following: Peripheral vascular injury; insufficient hemostasis or the presence of a small vascular hemorrhage in the pocket; large outer sheath-induced bleeding at the electrode entrance; unsuitable pocket size; prolonged use of aspirin or warfarin; elderly patient with low body weight; and allergies (6).

In the present study, data were collected from 339 patients who were subjected to permanent pacemaker implantation between June 2012 and June 2014. The predominant risk factors of pocket hematoma were identified using statistical analysis, which indicated a large-size pacemaker (39.63%), history of diabetes (22.22%), allergies (22.00%), and low BMI (15.79%) to be key risk factors.

Currently, with the widespread use of the electrocoagulation technique, rational use of antibiotics and the improvement of surgical technique, the incidence of pocket effusion or hematoma has been significantly reduced (10,11). However, a number of patients still suffer from this complication due to alternative causes, such as allergic reactions. Although allergic reactions to pacemakers are a relatively uncommon cause of pocket effusion or hematoma, diagnosis was often postponed and/or misinterpreted as a skin infection (12,13). It was difficult to reach a diagnosis of a pacemaker allergy for several reasons, even when infection had been dismissed as the cause. The most important reason was that allergic reactions to a pacemaker were rare and most reactions occurred between several weeks to a few months following implantation so the clinician may simply have failed to include it in a different diagnosis (12).

In the present study, the efficacy of promethazine administration was evaluated in 9 patients with medical histories of allergic reactions that were suffering from pocket effusion or hematoma. Promethazine was used to treat the allergy as the agent is able to act as a strong antagonist of the H1 receptor (antihistamine) (13). Sufficient clinical evidence supports the efficacy of promethazine for treating allergic reactions (14,15). The use of corticosteroids was not recommended in the present study as these may aggravate infection, diabetes, and slow the process of wound healing (16,17). The present findings revealed that the incidence of re-operations and the duration of hospital stay following promethazine treatment were significantly decreased.

Although one patient repeatedly suffered from pocket hematoma, histopathological examination revealed that granulation tissue proliferation with multinucleated giant cells was identified and no bacterial infection was present. Furthermore,

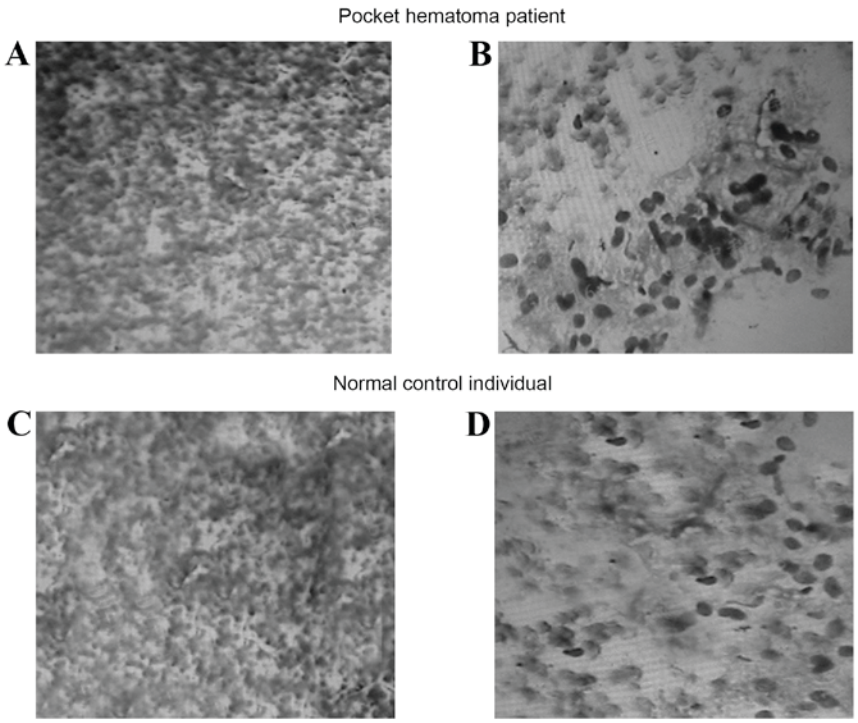

Figure 2. Blood fluid samples revealed that only lymphocytes and a limited number of tissue cells were indicated to be present (A and B) in a patient with pocket hematoma and (C and D) in a normal individual. (A) Magnification, x200; (B) magnification, x400; (C) magnification, x200; and (D) magnification, x400.

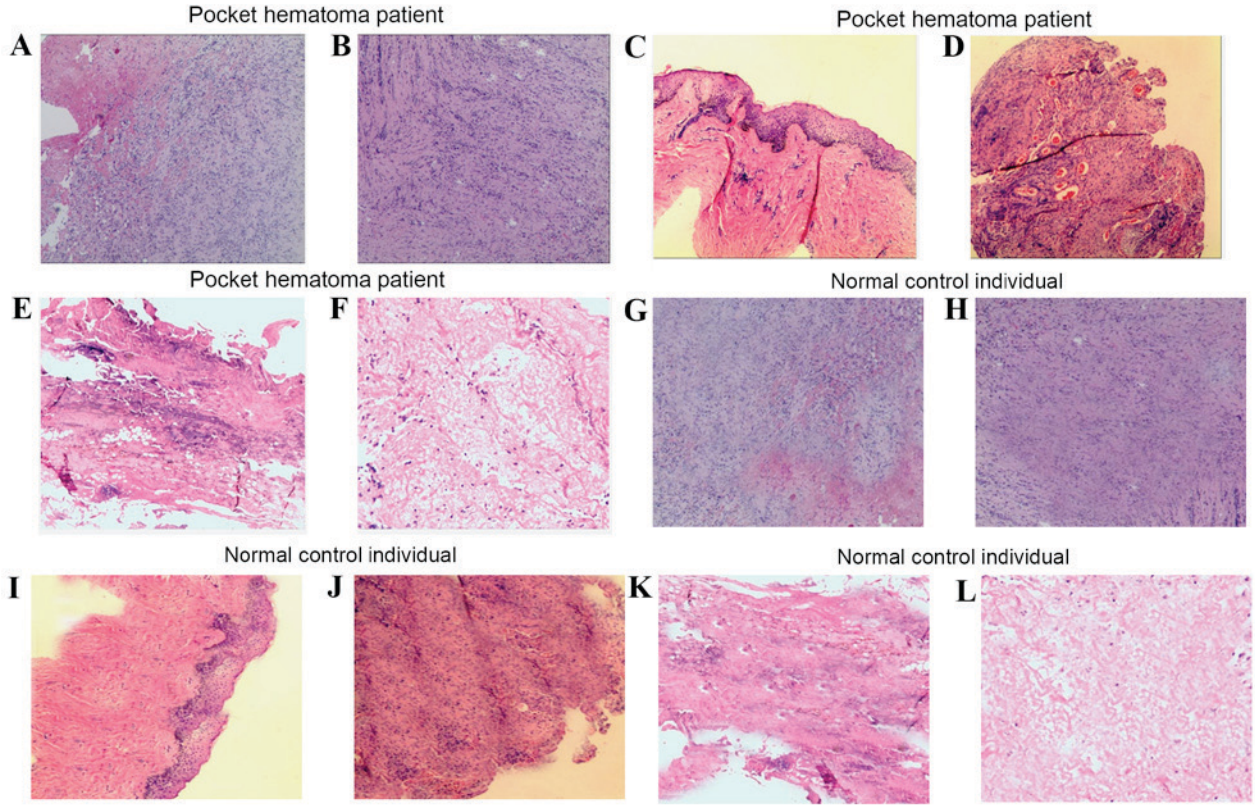

Figure 3. Histopathological examination (A-F) for pocket tissues and (G-L) in normal individual tissues. (A and B) Fibrous tissue with local superficial necrosis. A large number of lymphatic cells and a limited number of neutrophils and eosinophils were observed in the patient with allergic pocket hematoma. (A) Magnification, x200; (B) magnification, x400. (C and D) Scattered fibrous connective tissue was partially covered by squamous epithelium. Infiltration of inflammatory cells and dilation of the capillaries was detected. (C) Magnification, x200; (D) magnification, x400. (E and F) Acute inflammatory reaction and large numbers of inflammatory cells were observed in the patient with allergic pocket hematoma. (E) Magnification, x200; (F) Magnification, x400. (G and H) Fibrous tissue in normal individuals. (G) Magnification, x200; (H) Magnification, x400. (I and J) Scattered fibrous connective tissue in normal individuals. (I) Magnification, x200; (J) magnification, x400. (K and L) Acute inflammatory reaction and large numbers of inflammatory cells were not indicated in normal individuals. (K) Magnification, x200 and (L) magnification, x400.

the hematoma was absent following treatment with promethazine for one week, which further indicated the association between hematoma incidence and allergic reactions.

The present study suggested that histopathological examination and secretion culture are useful approaches. Histopathological examination demonstrated that samples predominantly contained lymphocytes and to a lesser extent erythrocytes and no infections were observed, indicating that allergic reactions may be a key risk factor in pocket effusion or hematoma development. Anti-allergy agents, such as promethazine or corticosteroid, may provide a novel method for the treatment of pocket effusion or hematoma. However, in our opinion, promethazine may be a superior treatment option compared with corticosteroids, due to the concerns on aggravation of infection, diabetes, and the decrease of wound healing associated with corticosteroid treatment (16,17).

The present study indicated various significant findings; however, there were also several limitations. Firstly, 33 patients developed allergic reactions and only 11 patients were diagnosed as allergic pocket hematoma. Furthermore, 2 patients were not able to receive the promethazine therapy as they did not consent to receiving injections of promethazine, therefore, only 9 patients with allergic pocket hematoma were administered promethazine in the present study. In subsequent studies, we would include a sufficient number patients with allergic pocket hematoma. Secondly, the present study is only a preliminary study of the effects of anti-allergic treatment on pocket-related complications following pacemaker implantation. Therefore, in this study, promethazine was administered to observe the anti-allergic effects alone. In future studies, the effects of alternative anti-platelet therapy should be considered. Thirdly, several antihistamines and multiple medications are effective to improve allergic reactions that have been indicated to be safer than promethazine (13-15). However, in our clinical experience, promethazine was revealed to be effective for the treatment of allergic reactions caused by the injection of traditional Chinese medicine, thus promethazine was used in the present study. In the present study, we discovered that anti-platelet therapy is unable to affect the incidence of pocket effusion or hematoma. Therefore, promethazine was applied as the therapeutic agent for this study. Moreover, in further studies, the effects of alternative antihistamines and medications should be investigated and compared with the effects of promethazine.

Although this is a nonrandomized, retrospective study from a single center with a relatively small number of patients, the present study provides important preliminary information that allergic reactions may be a risk factor of pocket effusion or hematoma and allergic reactions may be involved in the formation and repeated occurrence of pocket effusion or hematoma. To conclude, the application of anti-allergy therapy, such as promethazine, may be a useful method for the treatment of repeated pocket effusion or hematoma without infection.

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