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Correlation of tissue eosinophil count and chemosensory functions in patients with chronic rhinosinusitis with nasal polyps after endoscopic sinus surgery

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Abstract

Purpose To investigate the correlation of tissue eosinophil count and chemosensory functions in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) after endoscopic sinus surgery (ESS).

Methods This was a cross-sectional study including 40 patients with a history of ESS for CRSwNP recruited consecutively. Visual analog scale score and the Lund–Kennedy endoscopic score were recorded. Biopsies of the ethmoidal sinus mucosal were performed and evaluated. Chemosensory functions were measured by Sniffin' Sticks and chemosensory event-related potentials (CSERP). The associations between chemosensory functions and tissue eosinophil count were analyzed using Spearman correlation and partial correlation after adjusting the confounding factors. Kendall's tau-b correlation was performed between sneezing score and CSERP with ethyl alcohol (EAL) stimulation.

Results Olfactory and trigeminal nerve function was successfully evaluated using CSERP. Postoperative tissue eosinophil count was correlated with threshold (T) score (partial correlation coefficient $r=-0.460$, $p=0.012$) and CSERP peak latency for olfactory (N1: partial $r=0.471$, $p=0.010$; P2: partial $r=0.487$, $p=0.007$) and mixed olfactory–trigeminal (N1: partial $r=-0.516$, $p=0.008$; P2: partial $r=-0.590$, $p=0.002$). There were also correlations between T score and N1 latency with phenyl ethyl alcohol (PEA) (partial $r=-0.560$, $p<0.001$), between sneezing score and N1 latency with EAL (Kendall's tau-b $=-0.40$, $p=0.005$).

Conclusions Postoperative tissue eosinophilia is significantly associated with postoperative olfactory disorders as assessed by Sniffin' Sticks and CSERP peak latency. Furthermore, olfaction as measured by T score correlates with olfactory ERP latency in inflammation-associated olfactory dysfunction. Trigeminal sensitivity also appears to relate to tissue eosinophilia, indicating mucosal inflammation can affect both sensory systems in the nose.

Keywords Rhinosinusitis · Eosinophil · Smell · Trigeminal nerve · Olfactory test · Event-related potentials

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is often characterized by type 2 helper T cell (Th2) inflammation with mucosal eosinophilia as a major pathological hallmark [1, 2]; especially when olfactory disorders occur, quality of life in CRSwNP patients is greatly impaired [3]. Endoscopic sinus surgery (ESS) is an effective treatment of CRSwNP [4]; however, its positive effects on olfaction often are temporary and olfaction of some CRSwNP patients deteriorates again after surgery [5, 6]. The extent of postoperative eosinophilic inflammation contribution is unclear. Only a few studies report that preoperative tissue eosinophilia affect postoperative olfactory fluctuation

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[7], and most of inflammation-associated olfaction was based on self-reports and/or psychophysical tests (such as the UPSIT or the Sniffin' Sticks test). Due to subjective assessment, the conclusions might be not accurate [8]. The relationship between postoperative olfactory function and postoperative tissue eosinophilia has not been reported.

In addition, intranasal trigeminal function plays an important role in sensing a variety of stimuli such as warmth, coolness, burning, stinging or itching [9]. Doerfler et al. found that local inflammatory mechanisms of the nasal mucosa affect the activation of trigeminal nerve endings, which is correlated with clinical symptoms in allergic rhinitis patients. They observed a shortening of the latencies of the chemosensory event-related potentials (CSERP) which seems to be associated with an allergen-related sensitization of trigeminal nerve endings [10]. It is unknown whether eosinophilia plays a significant role in intranasal trigeminal hyperexcitation.

Thus, the correlation between postoperative tissue eosinophil, olfactory function and trigeminal function is unclear. The aim of this study is to investigate whether postoperative tissue eosinophil count is related to chemosensory functions in patients with chronic rhinosinusitis with nasal polyps after ESS, especially using objective CSERP.

Materials and methods

Patients

This was a cross-sectional study. Forty patients with a history of ESS for CRSwNP and almost after at least 6-month routine postoperative care in our clinic were recruited consecutively in May 2018 at Beijing An Zhen Hospital. Only those patients who had not used intranasal or systemic glucocorticoids for at least 1 month were included. The biopsies were performed under nasal endoscopic settings in the clinic. The median time that the biopsies were performed was 23 (11, 31) months after surgery. Patients were excluded if they had fungal sinusitis, antrochoanal polyps, nasal and sinus tumors, primary ciliary dyskinesia, or nasal trauma. The diagnosis criteria for CRSwNP were based on the current European Position Paper on Rhinosinusitis and Nasal Polyps [3]. The diagnosis of allergic rhinitis was determined according to the current clinical practice guidelines [11]. The clinical diagnosis of asthma was based on 2011 global strategy guidelines for asthma management and prevention [12]. All patients provided written informed consent, and this study was approved by the Ethics Committee of Beijing An Zhen Hospital, Capital Medical University (NO. 2017032X).

Histological analysis

We performed endoscopic biopsies of the ethmoidal sinus mucosal tissue of all recruited postoperative patients in the clinic. Sections were processed using standard techniques and stained with hematoxylin–eosin. The total eosinophil count was assessed in five randomly selected high power fields (HPF, ×400). The examination was performed by two experienced pathologists who were blinded by the patients' data. If their counts were consistent (within 10% variation), the average number of eosinophils was calculated and used for subsequent analyses. If the results were inconsistent (the difference was more than 10%), the two pathologists reviewed the specimen together with a two headed microscope and reached an agreement in results. Typical histopathological manifestations of tissue eosinophilia are shown (Fig. 1).

Visual analog scale

We used the visual analog scale (VAS) to evaluate subjective symptoms. The scores on VAS ranged from 0 to 10, with 0 representing no complaints and 10 representing the worst situation [13]. Five major symptoms were evaluated: sneezing, nasal obstruction, rhinorrhea, facial pressure or pain and loss of smell.

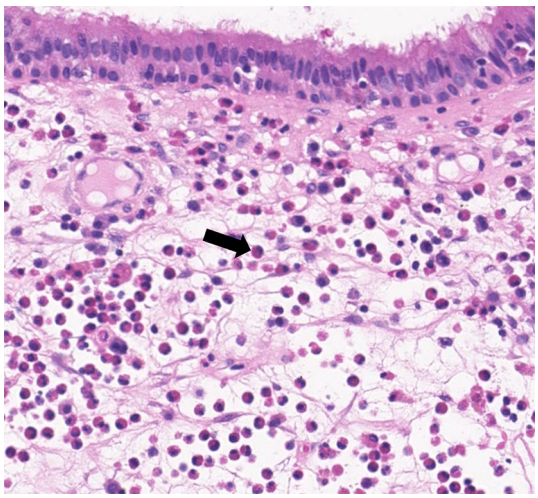

Fig. 1 Typical histopathologic manifestations of tissue eosinophilia (hematoxylin–eosin, original magnification ×200/HPF). Abundant eosinophils and a few neutrophils, plasma cells and lymphocytes in the section (eosinophil indicated by black arrows). *HPF* high power field

Lund–Kennedy endoscopic score

The nasal endoscopic findings were evaluated by the Lund–Kennedy endoscopic score (LKES) system, which included the following signs: polyps (scores of 0, none; 1, middle meatus; 2, beyond middle meatus), discharge (0, none; 1, clear and thin; 2, thick and purulent), edema (0, absent; 1, mild; 2, severe), scarring (0, absent; 1, mild; 2, severe) and crusting (0, absent; 1, mild; 2, severe) [14]. We calculated the total score of the right and left nasal cavities together for each sign. All the scores were determined by a professional otolaryngologist who was blinded to the results of symptom questionnaires.

Psychophysical olfactory function test

Olfactory function was quantified in 40 participants after surgery using the Sniffin' Sticks tests, which consist of three subtests [15]: odor threshold test, odor discrimination test, and identification test. We started with the odor threshold task, in which subjects had to distinguish the pen (with increasing concentrations of phenyl ethyl alcohol, PEA) from the other two odorless pens, and subjects could sniff twice for each odor presentation Then, during the odor discrimination task, the subjects were asked to discriminate one different odor from two identical odors. The odor identification task was conducted with 16 pens of different odors with a list of four descriptors for reference. When subjects smelled a certain odor pen, they had to choose an answer from the list. The maximum score on each test (threshold–discrimination–identification) was 16 points. The sum of the three tests constituted the TDI score with a maximum of 48 points [16].

Electrophysiological olfactory and trigeminal function tests

Electrophysiological clinical tests with olfactory and trigeminal stimuli were applied using a computer-controlled olfactometer based on air dilution olfactometry (OL006; Burghart, Wedel, Germany). When the subjects were given the special odor at the nostril, the olfactory and trigeminal receptors in the olfactory epithelium were activated, and the electrophysiological responses evoked are called olfactory event-related potentials (oERP) and trigeminal event-related potentials (tERP) [17]. During stimulation, the airflow (8 l/min), temperature (36 °C), and humidity (80% relative humidity) remained constant. OERP were obtained separately for each nostril using phenyl ethyl alcohol (PEA, 40% v/v) as a pleasant, rose-like odorant. To produce a mixed trigeminal–olfactory sensory stimulus, ethyl alcohol (EAL, 30% v/v) was used.

A total of 33 PEA stimuli and 32 EAL stimuli were presented to each subject's nostrils. The odor stimuli were given for 200 ms, with an inter-stimulus interval of 15 s to minimize olfactory adaptation. Each odor stimulus was delivered with a 4 cm Teflon tube with an inner diameter of 5.5 mm. EEG was recorded at a 250 Hz sampling rate from five positions (C3, C4, Fz, Cz and Pz) according to the international 10/20 system and referenced to an electrode at the inion (bandpass 0.1–30 Hz).

CSERP were recorded in a quiet and well-ventilated room. Eye movements and eyeblinks were minimized by asking subjects to refrain from blinking. To avoid auditory stimuli, the subjects were isolated with a 60-dB binaural white noise presented through headphones. We obtained 2048 ms records that were used for off-line data analysis. Subsequently, the latencies of the two base-to-peak amplitudes (L-N1 and L-P2) were measured relative to stimulus onset. Two base-to-peak amplitudes (N1 and P2) were also evaluated.

Chemosensory event-related potentials analyses

The largest amplitudes of CSERP were seen at C_Z. Because of artifacts (motor artifacts, eyeblinks, etc.), not all recordings could be used to analyze at all recording sites. Each record which was disturbed by eyeblinks or other motor artifacts was discarded from the average, and if averaged responses with eyeblinks exceeded 50 uV in the eye channel, we also deleted them to avoid interference for further analysis. Hence, CSERP were obtained by averaging 10–30 artifact-free electroencephalographic epochs following chemosensory stimulation [18]. Two distinct peaks can be identified, consisting of a negative component occurring between 320 and 450 ms after stimulus onset (often referred to as N1), followed by a positive component occurring between 530 and 800 ms after stimulus onset (often referred to as P2) [19]. Two experienced physicians took part in selecting waveforms by standardization and analyzed the latency and amplitude. At last, CSERP from 37 patients could be used. OERP and tERP waveforms for one CRSwNP postoperative subject and data of CSERP are, respectively, shown in Fig. 2 and Table 1.

Statistical analyses

The results are presented as means and standard deviations when quantitative data were normally distributed, while non-normally distributed data are expressed as medians and quartiles (P_{25}, P_{75}). Normal distribution was determined by the Kolmogorov–Smirnov test. Dichotomous variables were expressed by frequencies and percentage.

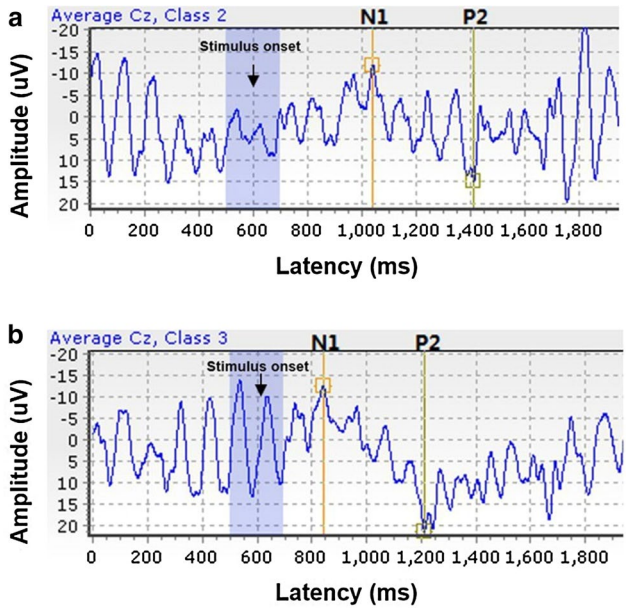

Fig. 2 CSERP obtained using averaged responses at *Cz* in an eosinophilia patient. **a** oERPs recording by PEA stimuli, two distinct peak identified, N1 (latency: 490 ms; amplitude: − 12 uV) and P2 (latency: 86 ms; amplitude: 14 uV); **b** tERPs recording by EAL stimuli, two distinct peak identified, N1 (latency: 294 ms; amplitude: − 12 uV) and P2 (latency: 661 ms; amplitude: 21 uV). *oERP* olfactory event-related potentials, *tERP* trigeminal event related potentials

Spearman correlation analysis was then carried out to analyze the relationship between tissue eosinophil count, Sniffin' Sticks score, and CSERP parameters. Kendall's tau-b is a robust rank-based correlation test used in analyzing sneezing VAS score and CSERP parameters. After adjusting for the covariates (age, gender, drinking, smoking, allergic rhinitis, asthma, postoperative time and Lund–Kennedy endoscopic score), partial correlation coefficients were calculated. Statistical analyses were performed using SPSS software for Windows (version 20.0, SPSS Inc., Chicago, Illinois). A probability value of < 0.05 in two side was considered statistically significant in all analyses.

Results

Baseline clinical characteristics

Among the 40 patients, there were 27 males and 13 females. The average age was 49 ± 10 years, including 13 (32.5%) smokers and 6 (15.0%) drinkers. In addition, there were 28 (70.0%) CRSwNP patients who had allergic rhinitis and 7 (17.5%) patients with asthma. The basic demographic and clinical information of patients is shown in Table 2.

Correlation between tissue eosinophilia, olfactory function, ERP parameters and sneezing

The results of correlation analyses and partial correlation analyses after adjusting for the covariates (age, gender, drinking, smoking, allergic rhinitis, asthma, postoperative time and Lund–Kennedy endoscopic score) were consistent with unadjusted results (Table 3). Tissue eosinophil count was correlated with T score (partial correlation coefficient $r = -0.460$, $p = 0.012$), but not D/I ($p > 0.05$), and also with CSERP peak latency N1 and P2 for olfactory stimulation with PEA (N1: partial $r = 0.471$, $p = 0.010$; P2: partial $r = 0.487$, $p = 0.007$) and EAL (N1: partial $r = -0.516$, $p = 0.008$; P2: partial $r = -0.590$, $p = 0.002$) stimuli, but not CSERP amplitudes ($p > 0.05$). Also, there was a strong negative correlation between T score and CSERP peak latency N1 for olfactory stimulation with PEA ($r = -0.560$, $p < 0.001$). In addition, there was a negative correlation between sneezing VAS score and CSERP latency with EAL stimuli (Kendall's tau-b $= -0.400$, $p = 0.005$).

Discussion

Olfactory disorders still are a major problem faced by CRSwNP patients after ESS. However, the etiology of postoperative olfactory dysfunction remains unclear. Few studies have examined eosinophilia as a major factor contributing to olfactory deterioration following temporary

Table 1 Latency and amplitude of CSERP with PEA and EAL stimuli in 37 postoperative patients

CSERP median (IQR)	PEA		EAL	
	N1	P2	N1	P2
Latency (ms)	360.0 (303.0, 425.0)	540.0 (478.0, 603.0)	413.0 (333.0, 503.0)	628.5 (529.5, 694.3)
Amplitude (uV)	− 10.0 (− 12.0, − 8.0)	7.0 (5.0, 10.0)	− 11.0 (− 15.0, − 9.0)	7.0 (4.3, 12.0)

Data are shown as median (IQR) with non-normal distribution. *N1* one distinct peak consisting of a negative component occurring between 320 and 450 ms after stimulus onset, *P2* another distinct peak following N1 as a positive component occurring between 530 and 800 ms after stimulus onset

CSERP chemosensory event-related potentials, *PEA* phenyl ethyl alcohol, *EAL* ethyl alcohol

Table 2 Patient characteristics

Variables	Patients ($n=40$)
Age, mean ± SD, years	49.0 ± 10.1
Male, *n* (%)	27 (67.5)
Smoking, *n* (%)	13 (32.5)
Drinking, *n* (%)	6 (15.0)
Allergic rhinitis, *n* (%)	28 (70.0)
Asthma, *n* (%)	7 (17.5)
Postoperative time (months), median (IQR)	23.0 (11.0, 31.0)
Lund–Kennedy endoscopic score, median (IQR)	
Total	6.00 (3.00, 9.00)
Polyps	0.00 (0.00, 2.00)
Edema	2.00 (0.50, 4.00)
Discharge	2.00 (2.00, 2.00)
Scarring	0.00 (0.00, 2.00)
Crusting	0.00 (0.00, 1.50)
Symptom VAS score, median (IQR)	
Sneeze	1.00 (0.00, 1.75)
Nasal obstructive	1.00 (0.00, 2.00)
Rhinorrhea	1.00 (0.00, 2.00)
Facial pressure or pain	0.50 (0.00, 2.75)
Loss of smell	3.00 (1.00, 5.00)

Data are shown as median (IQR) with non-normal distribution and mean (SD) with normal distribution

CRSwNP chronic rhinosinusitis with nasal polyps, *IQR* inter-quartile range, *SD* standard deviation, *VAS* visual analog scale

Table 3 Correlation coefficients between tissue eosinophil count and CSERP parameters

Variables	Unadjusted		Adjusted[a]	
	r	*p*	*r*	*p*
PEA				
N1				
Latency (ms)	0.530	< 0.001	0.471	0.010
Amplitude (uV)	0.130	0.713	0.069	0.720
P2				
Latency (ms)	0.380	0.020	0.487	0.007
Amplitude (uV)	0.213	0.206	0.213	0.267
EAL				
N1				
Latency (ms)	− 0.540	< 0.001	− 0.516	0.008
Amplitude (uV)	− 0.308	0.081	− 0.035	0.868
P2				
Latency (ms)	− 0.500	0.003	− 0.590	0.002
Amplitude (uV)	0.043	0.810	0.090	0.663

[a]Partial correlation, adjusted for age (years), gender (M/W), drinking (yes/no), smoking (yes/no), allergic rhinitis (yes/no), asthma (yes/no), postoperative time (months) and Lund–Kennedy endoscopic score. *N1* one distinct peak consisting of a negative component occurring between 320 and 450 ms after stimulus onset, *P2* another distinct peak following N1 as a positive component occurring between 530 and 800 ms after stimulus onset

CSERP chemosensory event-related potentials, *PEA* phenyl ethyl alcohol, *EAL* ethyl alcohol

improvement after surgery. The present research shows that postoperative tissue eosinophilia is associated with postoperative odor threshold score, but not discrimination or identification. This result is consistent with previous research findings: olfactory dysfunction related to nasal inflammation causes impaired odor detection. Indeed, threshold is thought to best reflect peripheral olfactory function, whereas the suprathreshold test (e.g., discrimination or identification) might better reflect central olfactory processing [20–22]. Also, in our study we find that there is a strong negative correlation between odor threshold and ERP latency to PEA. Thus, chemosensory ERPs are an effective way to assess olfactory function in a way that is consistent with the Sniffin' Sticks olfactory function test. Moreover, we found that higher numbers in tissue eosinophils are associated with increased oERP latency. Previous work on this topic has been limited to self-report and psychophysical tests which are semi-objective. Here, we are the first to assess olfactory function after surgery through both psychophysical and objective olfactory tests.

Taken together, our results show that postoperative tissue eosinophils may play an important role in olfactory disorders after surgery as assessed by CSERP. CSERP latency can more accurately reflect the effect of eosinophilia on olfaction in patients after surgery for CRSwNP. These findings support a role for eosinophilia in prognosis of olfaction after nasal polyp surgery. Indeed, eosinophils or eosinophil-associated cytokines have been increasingly recognized to play an important role in inflammatory olfactory disorders. As we know, eosinophil granule proteins are neurotoxic, suggesting that these eosinophil secretory products could damage olfactory neurons. Hauser et al. reported that ethmoid bulla eosinophilia is associated with olfactory loss in CRSwNP, independent of disease severity [23]. Another recent study showed that IL-2, IL-5, IL-6, IL-10, and IL-13 in olfactory cleft mucus are associated with reduced olfactory function in CRS patients [24]. Recently, mepolizumab, as a monoclonal antibody to IL-5, has been found to improve olfaction in patients with severe nasal polyps [25].

Previous studies have suggested a possible role for eosinophil or eosinophil-associated cytokines in CRS-associated olfactory loss. They may destroy the olfactory epithelium and cause apoptosis of olfactory neurons. We speculate that these may be the mechanisms that result in prolonged oERP latency. However, the amplitudes of N1/P2 showed no statistical association with tissue eosinophils by CSERP. Latencies may be relatively stable compared with the amplitudes. Pause et al. showed that the N1 amplitude does not depend

on odor concentration as pure olfactory stimulation does. Additionally, the latencies of the N1 wave became shorter with increased concentrations of olfactory odors [26]. It is known that early components of the potential (P1 and N1) mainly represent exogenous characteristics of the stimulus, e.g., stimulus intensity or stimulus quality [9]. To some degree, they can be viewed as a reflection of processes at the receptor level. In addition, it is hypothesized that patients with neurodegenerative diseases have decreased amplitudes of N1P2 in CSERP [18]. In summary, inflammation in the nose is likely to affect olfaction by a number of mechanisms. Although olfactory function can be significantly improved by treatment with steroids and/or with ESS, olfaction associated with CRSwNP tends to be decline following temporary postoperative improvement [27–30]. One of the major hypotheses is that nasal mucosal eosinophilic inflammation may arise again long after surgery. Our data support this concept. Additional study is needed to delineate the mechanisms that underlie this process.

Activation of trigeminal nerve endings can be recorded by CSERP. Most odorants not only activate the olfactory neurons, but also stimulate the trigeminal neurons [31–33]. In our study, PEA is used as a pure olfactory nerve activator, and anhydrous ethanol stimulator mainly activates trigeminal nerves and is used as a trigeminal activator. In our study, the tERPs N1/P2 peak latencies are strongly correlated with tissue eosinophils. Also, we find that increased sneezing score was associated with shortened ERP latency by EAL, which is consistent with increased trigeminal nerve sensitivity reflected by latencies shortening. This result is in line with the findings of Doerfler et al., who demonstrated that inflammatory conditions shorten tERP latencies and correlate with nasal itching and sneezing [10]. However, limited evidences support shortening latencies in N1P2 induced by eosinophil and or eosinophil-related degranulation protein. In fact, in asthma or eosinophilic esophagus (EOE), some studies show regulation of sensitivity of sensory nerves lying in lower airway or esophagus mucosa, mediated by eosinophil and or eosinophil-related degranulation protein [34]. Eosinophils can increase airway sensory nerve density in mice and further affect airway hyperreactivity [35]. However, little is known about effects of eosinophils on trigeminal nerve endings. We are the first to observe the shortened latencies in N1P2 by EAL, which is correlated with tissue eosinophils. Future studies will focus on the effects of eosinophil-related cytokines on trigeminal nerve sensitivity and the interaction between eosinophil-related cytokines and trigeminal nerve receptors and even exploring signaling pathways involved in inflammation-induced nerve hypersensitivity.

Further studies are needed to test the preoperative tissue eosinophil and chemosensory functions and explore their correlation. The changes and comparison between pre- and postoperation by CSERP are also needed to be analyzed. Some studies have stated that the sensitivity of trigeminal nerve endings could be affected by ESS. Monitoring whether the surgery affects the sensitivity of the trigeminal nerve would shed light on fluctuating olfaction after surgery. More information is needed on eosinophil-related cytokines on chemosensory functions [36, 37]. Finally, identification of mechanisms underlying inflammatory olfactory loss is needed to advance care.

Conclusion

Trigeminal and olfactory functions as measured by CSERP are affected by tissue eosinophilia after sinus surgery. CSERP appears to be an objective method for assessing olfactory and trigeminal responses in patients after ESS for CRSwNP.

Author contribution TH and LZ designed the study. CH analyzed the data. WY and YW performed histopathological analysis. LZ, PH and ZS wrote the manuscript. LZ, CH, XH, DW, HS and XY collected the clinical data and followed up with the patients. TH, YW read and revised the manuscript. All authors have read and approved the final manuscript.

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Compliance with ethical standards

Financial disclosure There are no financial disclosures of the authors.

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Ethics Committee of Beijing An Zhen Hospital, Capital Medical University, and had been performed in accordance with the ethical standards as laid down in the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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