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# Primary Hyper-IgE-Related Salivary Gland Disease: A New Disease Entity

Wen-Xuan Zhu, DDS; Yan-Yan Zhang, DDS; Yan Gao, PhD; Yan Chen, DDS; Zu-Yan Zhang, DDS; Hong Hua, DDS; Guang-Yan Yu, DDS, PhD

**Objectives:** To clarify the clinicopathological characteristics of primary hyper-IgE-related salivary gland disease (PHIESD), which is a newly proposed entity.

**Methods:** Fifteen consecutive patients pathologically diagnosed with chronic sialadenitis were enrolled, and their clinicopathological features were comprehensively analyzed. Inclusion criteria: (1) multiple salivary gland enlargement; (2) elevated serum IgE and/or IgE-positive cell infiltration in salivary gland tissues; (3) histology-confirmed lymphoplasmacytic infiltration; (4) exclusion of other known diseases.

**Results:** The male-to-female ratio was 5:10. The median age was 21 (range, 3–63) years. The average number of affected glands was 3.7 ± 1.4. Submandibular, parotid, and sublingual glands were involved in 15, 8, and 2 patients, respectively. Comorbid diseases included allergic diseases in seven patients and autoimmune diseases in two. Elevated serum IgE (median 175 kU/L) was seen in all patients. Serum IgG4 was slightly elevated in three patients. Histologically, most patients had mild lesions, including mild lymphocyte infiltration (60%) and focal fibrosis (66.7%). Lymphoid follicular formation (53.3%), moderate to severe lymphocytic inflammation (40%) and severe fibrosis (33.3%) were also observed. Immunohistochemically, IgE-positive cells infiltrated mainly around the ducts, with scattered infiltration of IgG4-positive, mast, and interleukin-4 positive cells. During follow-up (median, 46 months) of ten patients without intervention and two with immunosuppressive therapy, no significant changes in gland size or serum IgE level were noted.

**Conclusions:** PHIESD manifests as homogeneous enlargement of multiple salivary glands and elevated serum IgE. Histopathology further verifies the diagnosis. It might be associated with anaphylaxis or autoimmune dysfunction. Conservative treatment is suggested.

**Key Words:** allergy, autoimmune, hyper-IgE, salivary gland, sialadenitis.

**Level of Evidence:** 4

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## INTRODUCTION

In recent years, a group of salivary gland inflammatory diseases with elevated serum or tissue immunoglobulin E (IgE) has been discovered. The group includes IgG4-related sialadenitis (IgG4-RS),[1] Kimura's disease involved salivary gland,[2,3] and eosinophilic sialodochitis (ES),[4] which could be jointly named hyper-IgE-related salivary gland diseases. These diseases share clinicopathological features such as salivary gland enlargement, comorbidity with allergic diseases, elevated serum IgE, peripheral blood eosinophilia, tissue lymphoplasmacytic infiltration, and increased IgE-positive cell infiltration.[5–7]

From the Department of Oral and Maxillofacial Surgery (W.-X.Z., Y.-Y.Z., G.-Y.Y.), Peking University School and Hospital of Stomatology & National Center of Stomatology & National Clinical Research Center for Oral Disease & National Engineering Research Center of Oral Biomaterials and Digital Medical Devices & Beijing Key Laboratory of Digital Stomatology & Research Center of Engineering and Technology for Computerized Dentistry Ministry of Health & NMPA Key Laboratory for Dental Materials, Beijing, People's Republic of China; Department of Oral Pathology (Y.G., Y.C.), Peking University School and Hospital of Stomatology & National Center of Stomatology & National Clinical Research Center for Oral Disease & National Engineering Research Center of Oral Biomaterials and Digital Medical Devices & Beijing Key Laboratory of Digital Stomatology & Research Center of Engineering and Technology for Computerized Dentistry Ministry of Health & NMPA Key Laboratory for Dental Materials, Beijing, People's Republic of China; Department of Oral Radiology (Z.-Y.Z.), Peking University School and Hospital of Stomatology & National Center of Stomatology & National Clinical Research Center for Oral Disease & National Engineering Research Center of Oral Biomaterials and Digital Medical Devices & Beijing Key Laboratory of Digital Stomatology & Research Center of Engineering and Technology for Computerized Dentistry Ministry of Health & NMPA Key Laboratory for Dental Materials, Beijing, People's Republic of China; and the Department of Oral Medicine (H.H.), Peking University School and Hospital of Stomatology & National Center of Stomatology & National Clinical Research Center for Oral Disease & National Engineering Research Center of Oral Biomaterials and Digital Medical Devices & Beijing Key Laboratory of Digital Stomatology & Research Center of Engineering and Technology for Computerized Dentistry Ministry of Health & NMPA Key Laboratory for Dental Materials, Beijing, People's Republic of China.

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Send correspondence to Guang-Yan Yu, DDS, PhD, Department of Oral and Maxillofacial Surgery, Peking University School of Stomatology, No.22, Zhongguancun South Avenue, Haidian District, Beijing 100081, People's Republic of China.

E-mail: gyyu@263.net

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Elevated IgE is an important indicator of diagnosis and prognosis and plays an important role in the pathogenesis of such diseases.

IgE carries reagin activity, has immense importance for the pathogenesis, diagnosis, treatment of allergic diseases, and mediates autoimmune diseases.[8–10] Most IgE binds to its high-affinity surface receptor (FcεRI) on mast cells in the subcutaneous and submucosal tissues and basophils in the blood, causing the release of mediators that drive the symptoms of allergic inflammation.[9,11] Several studies have shown that IgE either specifically binds to self-antigens or cross-reacts with environmental substances.[11] This binding activity incriminates IgE autoantibodies as central in the pathogenesis of inflammatory autoimmune disorders such as chronic urticaria, rheumatoid arthritis, bullous pemphigoid, and systemic lupus erythematosus.[12,13]

IgG4-related disease is a multi-organ immune-mediated disease.[1] Kimura disease is a chronic inflammatory granulomatous disease-related to immune-mediated disorder,[2,3] and ES manifests as a specific type of sialadenitis related to allergy.[4] These diseases could be regarded as secondary hyper-IgE-related salivary gland diseases. However, we recently found a group of patients with a disease characterized by multiple enlarged salivary glands and elevated IgE in the serum and/or tissue, which could not be classified into any of the known diseases. The disease could be named as primary hyper-IgE-related salivary gland disease (PHIESD). The purpose of this study was to systematically investigate the clinical, laboratory, imaging, histopathological and immunopathological characteristics of this newly proposed entity.

## MATERIALS AND METHODS

The Ethics Committee for Human Experiments of Peking University School of Stomatology approved the study protocol (PKUSSIRB-201947099). Informed consent was obtained from all patients or their legal guardians.

### *Patient Selection and Study Design*

The clinical and histopathological records of 15 special patients with salivary gland enlargement at Peking University School of Stomatology from January 2014 to February 2021 were retrospectively collected. All patients satisfied the following criteria: (1) bilateral major salivary gland enlargement for more than three months; (2) increased serum IgE level or IgE positive cell infiltration in the salivary gland tissues; (3) histopathological examination showing lymphocyte and plasma cell infiltration, which can confirm the diagnosis of chronic sialadenitis, and exclude the suspicion of IgG4-RS,[5] Kimura's disease,[14] and eosinophilic sialodochitis, or other known diseases.[4] Two of the tissue samples were from parotid glands (PGs), and 13 from submandibular glands (SMGs). Tissue samples were acquired by glandular excision in one patient and incisional biopsy in the other 14. The patients' clinical, laboratory, radiological, histopathological and immunopathological data were reviewed and analyzed. An elevated peripheral blood eosinophil (PBE) count was defined as $>0.5 \times 10^9$ cells/L or > 5% of the leukocytes. An elevated serum total-IgE was defined, based on our institutional range, as >60 kU/L in 1–5-year-old patients, >90 kU/L in 6–9-year-old patients; >200 kU/L in 10–15-year-old children, and >100 kU/L in adults.

### *Histopathological Evaluation*

The hematoxylin and eosin-stained slides from all patients were reviewed, and the following histopathological features were recorded: (a) gland atrophy: 0, no atrophy; 1, occasional atrophic foci; 2, extensive moderate parenchyma atrophy; 3, extensive serious parenchyma atrophy; (b) fibrosis of the gland: 0, a small amount of fibrosis; 1, partial mild fibrosis; 2, extensive moderate fibrosis; 3, extensive serious fibrosis; (c) infiltration of lymphocytes: 0, scattered lymphocytes as seen in normal glands; 1, occasional focal distribution of lymphocytes; 2, extensive moderate

TABLE I.
Clinical and Laboratory Features of Primary Hyper-IgE-Related Salivary Gland Disease.

| Patient | Onset age (years) | Sex | Involved glands | Serum T-IgE (kU/L) | Serum IgG4 (mg/dL) | Comorbid allergic disease | Follow-up of Serum T-IgE (kU/L) |
|---|---|---|---|---|---|---|---|
| 1 | 64 | F | Bilateral SMG and LG | 146 | 127 | – | 135 |
| 2 | 3 | F | Bilateral SMG | 139 | 97.8 | Allergic rhinitis, urticaria | 227 |
| 3 | 55 | M | Bilateral SMG, PG, and LG | 117 | 134 | Allergic rhinitis | – |
| 4 | 54 | M | Bilateral SMG, right PG | 218 | 130 | – | 189 |
| 5 | 3 | F | Bilateral SMG | 346 | 28.5 | Atopic dermatitis | 253 |
| 6 | 23 | F | Bilateral SMG | 617 | 192 | Allergic rhinitis | 678 |
| 7 | 10 | F | Bilateral SMG, right PG | 67.8 | 11 | – | 63 |
| 8 | 13 | M | Bilateral SMG and SLG | 343 | 54 | – | 211 |
| 9 | 21 | F | Bilateral SMG, PG, and SLG | 238 | 303 | Urticaria | 210 |
| 10 | 57 | M | Bilateral SMG, PG, and LG | 142 | 87.8 | – | 153 |
| 11 | 3 | F | Bilateral SMG and PG | 148 | 120 | Allergic rhinitis | 102 |
| 12 | 48 | F | Bilateral SMG and LG | 467 | 40.1 | Allergic rhinitis | 410 |
| 13 | 13 | F | Bilateral SMG | 175 | 21.4 | – | 189 |
| 14 | 29 | M | Bilateral SMG and PG | 424 | 77.4 | – | – |
| 15 | 3 | F | Bilateral SMG and PG | 147 | 165 | – | – |

Elevated serum IgG4: >140 mg/dL.
F = female; LG = lacrimal gland; M = male; PG = parotid gland; SMG = submandibular gland; SLG = sublingual gland; T-IgE = total IgE.

infiltration of lymphocytes; 3, extensive serious infiltration of lymphocytes.[15] Follicular hyperplasia was recorded as present or absent. Two observers re-reviewed each slide and reached a consensus by discussion. Three high power fields (HPFs) with the greatest eosinophil density were selected and quantified (HPF area = 0.2375 $mm^2$).

### *Immunohistochemical Evaluation*

Tissue sections (4-μm thickness) were deparaffinized and rehydrated. Endogenous peroxidase activity was blocked with 3% $H_2O_2$. We used antibodies against human IgG (prediluted ZA0448, Zhongshan, Beijing, China), IgG4 (prediluted ZA0576, Zhongshan), IgE (prediluted ab75673, Abcam, Cambridge, UK), mast cell tryptase (diluted 1:1000, ab2378, Abcam), cluster of differentiation 21 (CD21; prediluted ZA0525, Zhongshan), IL-4 (diluted 1:200, ab239508, Abcam), IL-5 (26677-1-AP, Proteintech, Wuhan, China), IL-13 (diluted 1:200, ab106732, Abcam), and eotaxin (diluted 1:150, ab133604, Abcam). Antigen retrieval was achieved by treating the sections with a boiling citric acid buffer solution (0.01 mol/L, pH 6.0) for 10 min in a microwave oven. Negative controls were obtained using normal SMG tissue. Three identical HPFs with the greatest IgE-, tryptase-, IgG-, IgG4-, IL-4-, IL-5-, eotaxin-, and IL-13-positive cell density were selected and quantified using Image-Pro® Plus 6.0 (Media Cybernetics, Rockville, MD, USA). The ratio of IgG4+/IgG+ cells was calculated. The expression of IgE and CD21 in the germinal center was also observed.

### *Statistical Analyses*

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). The mean ± standard deviation or median (interquartile interval) was used for continuous variables, which were compared by independent samples *t*-test or Wilcoxon signed-rank test. Categorical variables were expressed as percentages and were compared using the chi-squared or Fisher's exact test. Differences with $p < 0.05$ were considered statistically significant.

## RESULTS

### *Clinical Features*

The male to female ratio among the 15 PHIESD patients was 5:10. The median onset age was 21 years (range, 3–63 years). The onset was mostly in children and youths, with seven of the patients being younger than 14 years old. The median duration from onset of clinical

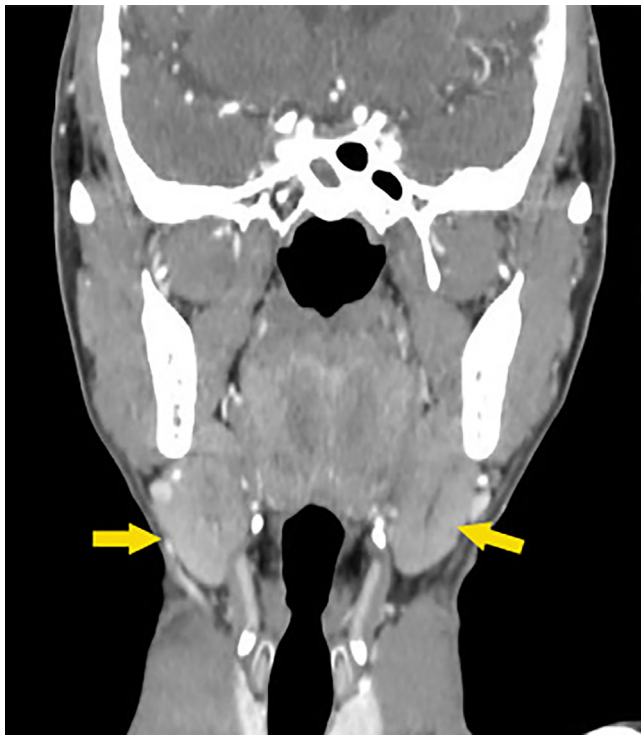

Fig. 2. Bilateral submandibular gland enlargements with homogeneous contrast enhancement on a coronal enhanced CT slice (arrows) [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

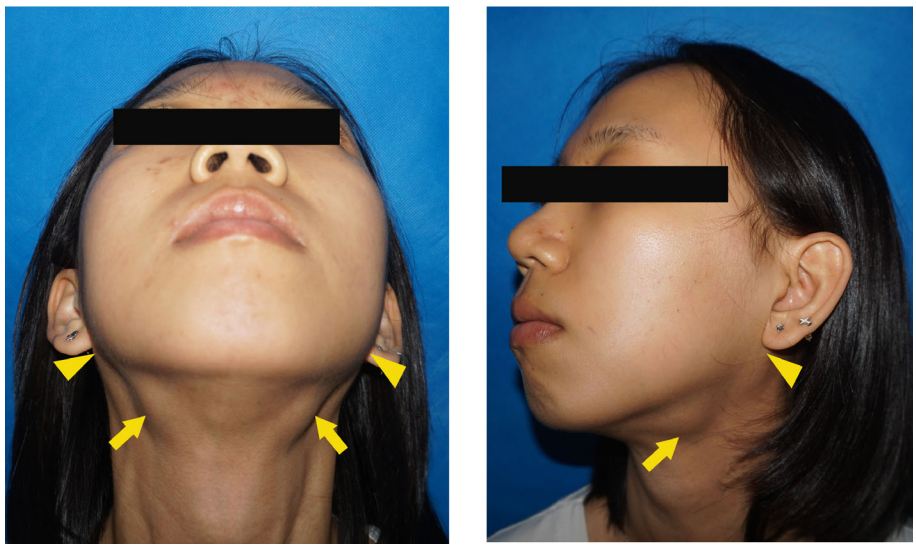

Fig. 1. Enlargement of the parotid glands (arrowheads) and submandibular glands (arrows) [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

signs to diagnosis was six months. The average number of affected glands was 3.7 ± 1.4 (Table I). The SMG, PG, lacrimal gland, and sublingual glands were involved in 15 (100%), 8 (53.3%), 5 (33.3%), and 2 (13.3%) patients, respectively. Bilateral involvement of major salivary glands was seen in all patients (100%; Fig. 1). All patients complained of painless enlargement of the involved glands with a distending feeling. Three (21.4%) patients had a history of remission, and six (42.9%) had mild xerostomia. Seven patients (46.7%) had comorbid allergic diseases, including allergic rhinitis ($n$ = 4, 26.7%) and atopic dermatitis or urticaria ($n$ = 3, 20%). (Table I) Two patients (13.3%) had an autoimmune disease, including rheumatoid arthritis and membranous nephropathy. Two patients (13.3%) had thyroid disorders. On palpation, all affected glands were diffusely enlarged without tenderness, and the texture was soft or toughened.

### *Laboratory Findings*

Serum total-IgE was elevated in all patients, with a median value of 175 kU/L (range, 67.8–617 kU/L). Four of the six patients with an allergic disease were positive for serum specific-IgE, and one patient without allergic diseases had slightly positive specific-IgE for food. No increase in peripheral blood eosinophil count was observed, with a median value of 2.0% (range, 0.6%–4.5%). The median serum IgG4 concentration was 97.8 mg/dL. It was only mildly elevated in three patients (20%). Two cases (13.3%) were positive for rheumatoid factor. The patients tested negative for antibodies of anti-Sjögren's syndrome type A and B antigen (-SSA and -SSB, respectively) (Table I).

### *Imaging Characteristics*

All 15 patients underwent spiral computed tomography (CT) examination, which displayed three-dimensional enlargement of all affected glands along with the original contour. Briefly, the affected glands showed homogeneous density, while tumoral lesions were never found (Fig. 2). Enhanced CT, performed in eight adult patients, showed moderate and uniformly distributed enhancement. Among these eight patients, the area of SMGs set

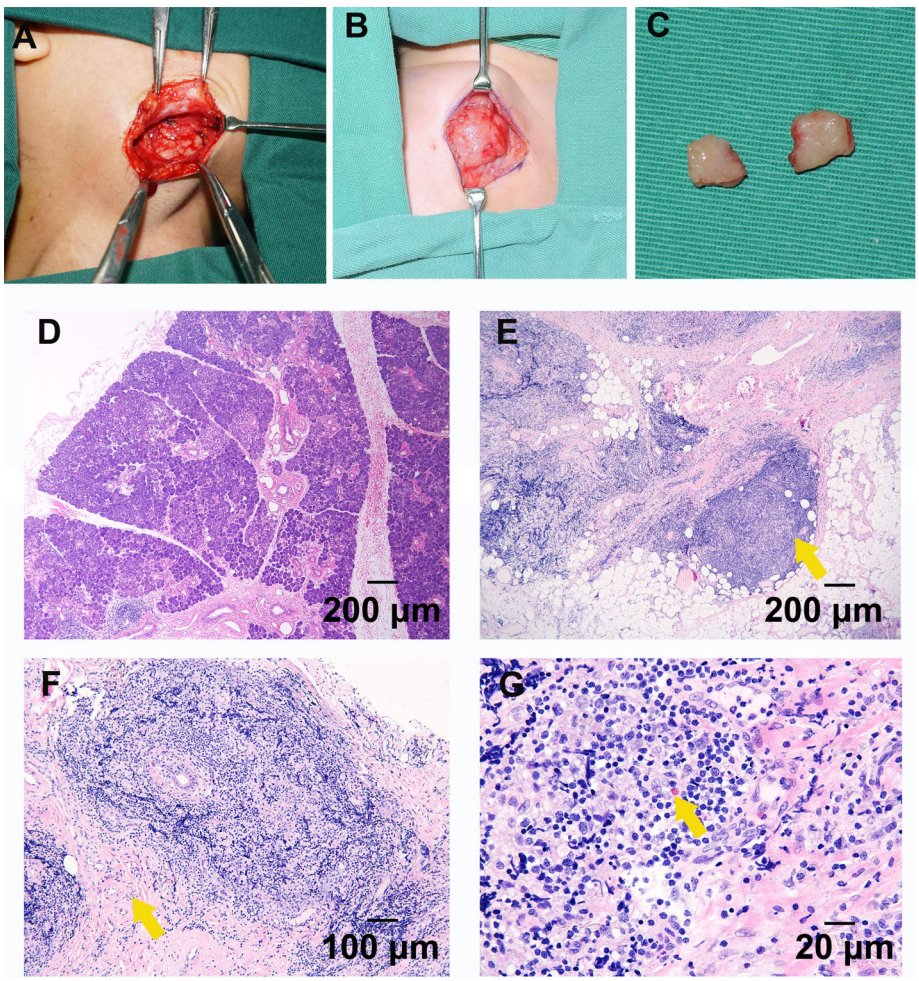


Fig. 3. Gross appearance and histopathological features. (A) ascertained glandular lobule structure. (B), (C) homogeneous and firm *in situ* (B) and *ex situ* (C) gland tissue. (D) mild lymphoplasmacytic inflammation. (E) severe lymphoplasmacytic inflammation without tissue atypia and lymphoid follicular formation (arrow). (F) extensive fibrosis (arrow). (G) mild eosinophil infiltration [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE II.
Histopathological and Immunochemical Features of Hyper-IgE-Related Salivary Gland Disease ($N = 15$).

| | |
|---|---|
| Histopathological features | |
| Eosinophils, cells/HPF, m (Q1–Q3) | 0 (0–0) |
| Grade of acinar atrophy | |
| 0 and 1, *n* (%) | 7 (46.7) |
| 2 and 3, *n* (%) | 8 (53.3) |
| Grade of fibrosis | |
| 0 and 1, *n* (%) | 10 (66.7) |
| 2 and 3, *n* (%) | 5 (33.3) |
| Grade of lymphocytic infiltration | |
| 0 and 1, *n* (%) | 9 (60) |
| 2 and 3, *n* (%) | 6 (40) |
| Follicular hyperplasia, *n* (%) | 8 (53.3) |
| Infiltration of eosinophils, *n* (%) | 3 (20) |
| Immunohistochemical features | |
| IgE+, cells/HPF, m (Q1–Q3) | 4 (0–11) |
| IgE+ reticular networks in GCs, *n* (%) | 3(20) |
| IgG+, cells/HPF | 51 ± 41.6 |
| IgG4+, cells/HPF | 11.5 ± 11.4 |
| Tryptase+, cells/HPF, m (Q1–Q3) | 5 (3–16) |
| CD21+, *n* (%) | 9 (60) |
| IL-4+, cells/HPF, m (Q1–Q3) | 5 (3–9) |

Unless otherwise stated, values are presented as mean ± standard deviation.

CD21 = cluster of differentiation 21; HPF = high power field; GC = germinal center; Ig = immunoglobulin; IL = interleukin.

through the full course of the main duct was calculated on sagittal views using the software provided by the manufacturer. These were compared to other 8 patients with comparable demographic features, who had normal SMGs and underwent CT scanning for other diseases. The results showed that the areas of the SMGs with PHIESD ($839.9 \pm 162.0$ mm$^2$) were significantly larger than the control group ($620.2 \pm 99.5$ mm$^2$, $p < 0.001$).

### *Histopathological and Immunohistochemical Features*

During the biopsies, the involved salivary glands were soft, and the glandular lobule structure could be ascertained in 12 patients during surgery (Fig. 3A). In the remaining three patients, gland tissue was homogeneous and firm (Fig. 3B,C). Histologically, the lesions in most patients were mild, and lobular structures were preserved. Seven patients (46.7%) showed no or occasional acinar atrophy, while moderate to serious acinar parenchyma atrophy was seen in eight patients (53.3%). Fibrosis and lymphocyte infiltration could be seen around the ducts. Nine patients (60%) showed mild (Fig. 3D), and six (40%) showed moderate to severe (Fig. 3E) lymphocytic inflammation, without atypia signs. The lymphoid follicular formation was observed in eight patients (53.3%; Fig. 3E). Focal and wide fibrosis (Fig. 3F) were respectively observed in ten (66.7%) and five (33.3%) patients. However, fibroblasts, storiform fibrosis, and periductal collagen sheath were absent. There was only one patient with marked and two with mild eosinophil infiltration (Fig. 3G, Table II).

Immunohistochemical staining showed mild to moderate IgE-positive cell infiltration, mainly around the ducts, and scattered IgE-positive cells throughout the interfollicular and atrophied acini area. Three (20%) of the patients had IgE-positive reticular networks in the germinal centers (Fig. 4A,B). Only slightly scattered or focally infiltrated IgG4-positive cells were observed (Fig. 4C), while IgG-positive cell infiltration was mild (Fig. 4D). Scattered tryptase-positive mast cells were mainly located in the periductal fibrosis areas (Fig. 4E). In nine patients, the lymphoid follicles showed a prominent network of CD21-positive dendritic reticular cells (Fig. 4F). (Table II) The IgE-positive reticular areas mostly overlapped with the CD21-positive areas. IL-4-positive cells were scattered through the tissue (Fig. 4G), while staining for IL-5 and IL-13 was negative (Fig. 4H,I).

### *Follow-up and Prognosis*

Twelve patients were closely followed up for 12–68 months (median 46 months). Among these, nine were followed up for more than two years. Ten patients without a comorbid autoimmune disease were followed up without intervention. They never felt pain in the affected glands, and the distending feeling was slightly relieved. Interestingly, the symptoms were relieved after avoiding exposure to allergens in two of the patients with allergic diseases. Clinical examination showed no significant changes in the gland 's sizes. Two patients experienced glucocorticoid and immunosuppressive therapy for a comorbid autoimmune disease, during which the feeling of gland distending was significantly relieved. Among these 12 cases, there was no significant change in the serum total-IgE value (median value: 175.0 vs. 199.5 kU/L, $p = 0.304$). In the remaining three patients, two were newly diagnosed and one was lost to follow-up.

## DISCUSSION

As a new entity, the clinicopathological characteristics of PHIESD need to be analyzed and summarized, and the treatment principles and prognosis need to be explored.

Demographically, PHIESD occurred mostly in youths, with children accounting for a large proportion of the patients. The clinical manifestation was mainly the asymptomatic enlargement of multiple salivary glands, often bilaterally, similar to secondary hyper-IgE-related salivary diseases, such as IgG4-RS and eosinophilic sialodochitis.[4,5] Although elevated total-IgE was a typical characteristic of PHIESD, the proportion of patients with a comorbid allergic disease (46.7%) was lower than in eosinophilic sialodochitis (>90%).[4] It was speculated that IgE-positive cell infiltration and elevated serum IgE might be associated with inherent abnormal immune regulation rather than an allergic reaction, similar to IgG4-RS.[6,16,17] The low incidence of allergic disease in

PHIESD might be due to inhibition of the passive anaphylactic reaction by an excess in low-affinity IgE.[18] The precise mechanism remains to be elucidated.

Histopathological manifestation revealed various degrees of lymphocyte infiltration and fibrosis, with seldomly observed eosinophils. However, the inflammatory response was mild in most cases, which was similar to early IgG4-RS lesions. Storiform fibrosis, a typical histologic feature of IgG4-RS, was absent, and only a few focal IgG4-positive cells were found. Nevertheless, whether these patients were at an early stage of IgG4-RS is still unknown. Hence, it is necessary to closely monitor their serum IgG4 level and the clinical appearance of their salivary glands. An increased serum IgG4 level accompanied by enlarged and hardened salivary glands and systemic manifestations might indicate a diagnosis of IgG4-RS.[5] In three patients, serum IgG4 level was slightly elevated, this might also be an attached phenomenon of PHIESD. The generation and class exchange of IgE are regulated by Th2 and Treg cells and their cytokines. These might be accompanied by a slight increase in IgG4.[19–24] Future studies are needed to test this hypothesis.

Most IgE-positive cells found in the salivary gland tissues were membrane IgE-positive cells, which might primarily represent immune cells with IgE attached to membranal receptors.[6] IL-4 is the main cytokine to induce IgE production, and the FcεRI on mast cells is the primary IgE receptor,[22,25] accounting for the scattered infiltration of IL-4-positive cells and mast cells. The absence of the allergy-related cytokines, IL-5 and IL-13, might be due to the gentle degree of the lesions or inactive IgE-related reactions in the local tissues. In patients with IgE-mediate disease, IgE production is observed in the peripheral blood and locally in various human tissues (e.g., nose and lungs),[11] influenced by genetic, racial, immune, and environmental factors.[10] Neither the precise sites nor the nature of the IgE-producing cells is known in PHIESD patients with no apparent allergic symptoms. Whether the elevated IgE is a side effect of allergy or a key mechanism driving the salivary gland enlargement needs to be further investigated.

The follow-up results showed that, over time, the swelling degree of the enlarged glands had decreased slightly, with no significant change in serum IgE levels. These findings indicate a relatively slow progression of the disease. It is worth studying whether this disease is self-limiting like juvenile recurrent parotitis, in which the symptoms resolve spontaneously as the childhood

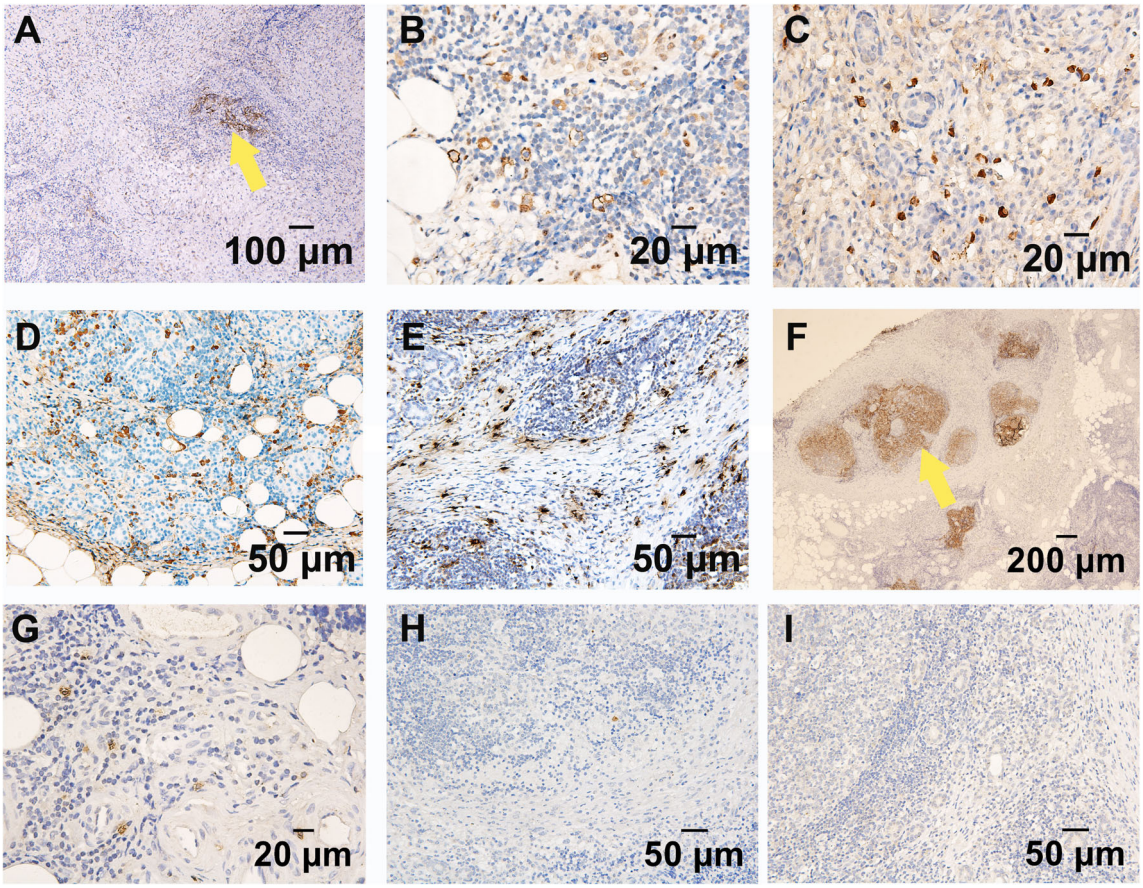


Fig. 4. Immunohistochemical features. (A) IgE-positive reticular networks in the germinal centers. (B) IgE-positive cell infiltration with cytoplasm or surface membrane staining. (C) scattered IgG4-positive cells. (D), focally distributed IgG-positive cells. (E) tryptase-positive mast cells distributed in the fibrotic areas. (F) CD21-positive cells in the germinal centers (arrow). (G) scattered IL4-positive cells. (H) negative expression of IL-5. (I) negative expression of IL-13. CD21, cluster of differentiation 21; IL, interleukin. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

immature immune system and defective regulatory functions mature with age.[26] Consequently, the intervention can be conservative, especially in children. Self-maintenance treatments, including daily glandular massage, sialagogues and gum chewing, which help resolve saliva retention and stimulate saliva secretion, are suggested if glandular distention symptoms persist. Allergen testing, various allergic factors avoidance, and appropriate anti-anaphylactic treatment are recommended to relieve apparent allergic symptoms. It should be emphasized that a close and extended follow-up is necessary to monitor the progression into IgG4-RS and other salivary diseases.

Our study has several limitations: (1) a bit small sample size; (2) absence of long-term follow-up records in several cases; (3) absence of allergen screening in some patients. Had these works been performed, a more profound understanding of the clinicopathological characteristics and treatment principles of the disease, and further insights into its relationship with allergy, could be achieved.

## CONCLUSIONS

PHIESD is a newly proposed salivary gland disease entity characterized by homogeneous enlargement of multiple salivary glands and elevated IgE levels. Histopathology can further verify the diagnosis. PHIESD might be associated with autoimmune disorders or allergic reactions. The disease progression is slow, and it could be treated conservatively. However, a close and extended follow-up is required for monitoring its possible progression to IgG4-RS.

Consent to participate: Informed consent was obtained from all individual participants or from the parents included in the study.

Consent for publish: Patients signed informed consent regarding publishing their data.

## DATA AVAILABILITY STATEMENT

All data used in the study are available from the corresponding author by request.

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