Int. J. Oral Maxillofac. Surg. 2021; xx: 1–4
https://doi.org/10.1016/j.ijom.2022.03.055, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Oral Medicine

Hyper-IgE syndrome caused by *DOCK8* mutation with a tumour-like lesion of the lip: a case report

W.-X. Zhu[a,b], Y.-Y. Liu[c], H. Hua[d], G.-Y. Yu[a]

[a]Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, Beijing, China; [b]Center of Stomatology, China–Japan Friendship Hospital, Beijing, China; [c]Department of Rheumatology and Immunology, Capital Medical University Affiliated Beijing Friendship Hospital, Beijing, China; [d]Department of Oral Medicine, Peking University School and Hospital of Stomatology, Beijing, China

W.-X. Zhu, Y.-Y. Liu, H. Hua, G.-Y. Yu: Hyper-IgE syndrome caused by DOCK8 mutation with a tumour-like lesion of the lip: a case report. Int. J. Oral Maxillofac. Surg. 2021; xx: 1–4.

Abstract. Autosomal recessive hyper-IgE syndrome caused by *DOCK8* gene mutation is an immunodeficiency. However, the presentation of a tumour-like lesion of the lip in autosomal recessive hyper-IgE syndrome has not yet been reported. This article reports the case of a 20-year-old man with autosomal recessive hyper-IgE syndrome who presented with a tumour-like lesion of the lip, and hyperplasia and erosion of the gingiva. The clinical manifestations included coarse face and neck skin, a diffuse tumour-like lesion on the upper lip showing a reddish erosive nodular surface with yellowish-white exudation, erosive buccal mucosa, and severe periodontitis. The swollen gingival and palatal mucosa indicated nodular hyperplasia and redness with pseudomembrane. The patient had a significantly increased peripheral blood eosinophil count and serum IgE level and an abnormal T lymphocyte count. His oral lesions improved markedly after prednisolone acetate use and local symptomatic treatment for 2 years. However, the patient unfortunately died of a cerebral infection 6 months after the oral lesions had resolved. The novel features of the labial tumour-like lesion described here extend our understanding of the manifestations of autosomal recessive hyper-IgE syndrome.

Keywords: Job syndrome; hyper-IgE syndrome; human *DOCK8* protein; mutation; mouth diseases.

Accepted for publication 17 March 2022
Available online xxxx

Introduction

Hyper-IgE syndrome (HIES), also called Job syndrome, is a rare primary immunodeficiency characterized by eczema, recurrent skin and pulmonary infections, an extremely elevated serum IgE level, and various connective tissue and skeletal abnormalities.[1] Individuals with HIES have a characteristic facial appearance and oral manifestations, including retained primary dentition, a high arched palate, oral mucosal and gingival variations, and recurrent oral candidiasis.[2] Both autosomal dominant (AD) HIES due to *STAT3* mutations and autosomal recessive (AR) HIES due to *DOCK8* and *TKY2* mutations have been reported.[1,3]

The DOCK8 protein plays an important role in cytoskeletal organization, affecting dendritic cell migration, the proliferation and apoptosis of T cells and B cells, and natural killer cell toxicity.[3,4] The pathogenesis of AR-HIES caused by *DOCK8* gene mutation is a progressive combined immunodeficiency involving viral skin infections and severe food allergies.[3] Nevertheless, the typical oral and maxillofacial findings in HIES patients with DOCK8 deficiency have rarely been reported.

Case report

A 20-year-old man was referred to the Department of Oral and Maxillofacial Surgery, Peking University School of Stomatology in November 2018, due to a mass of the upper lip and gingival

0901-5027/xx0001 + 04

Please cite this article as: W.-X. Zhu, Y.-Y. Liu, H. Hua et al., Hyper-IgE syndrome caused by *DOCK8* mutation with a tumour-like lesion of the lip: a case report, Int. J. Oral Maxillofac. Surg, https://doi.org/10.1016/j.ijom.2022.03.055

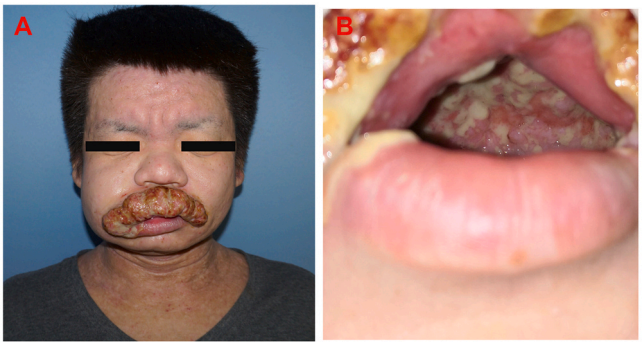

Fig. 1. Clinical manifestations in the oral and maxillofacial region. (A) The diffuse tumour-like lesion of the upper lip. The skin of the patient's face and neck was coarse; he had a slightly prominent forehead, broad nasal bridge with nasal tip hypertrophy, and a widened orbital distance. (B) The palatal mucosa showed thickness with a nodular appearance and redness with pseudomembrane.

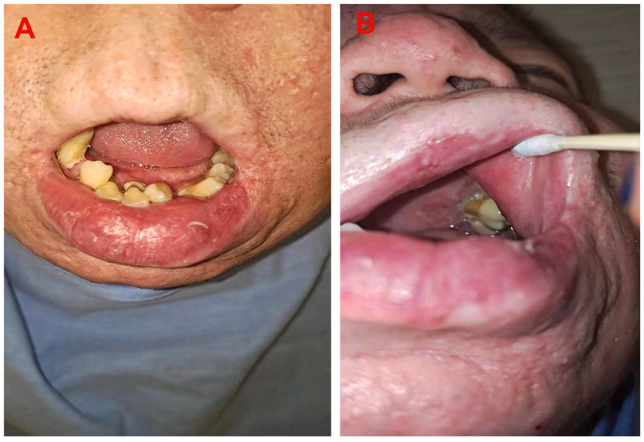

Fig. 2. Clinical signs after treatment. (A) The tumour-like lesion of the lip disappeared. (B) The nodular hyperplasia of the palatal mucosa was reduced.

swelling for 6 months (Fig. 1). He had been diagnosed with HIES based on the detection of *DOCK8* gene mutation at the age of 12 years. During the period between 12 and 18 years of age, he had developed severe pneumonia of the immunocompromised host. After comprehensive treatment with antibiotics, intravenous hydrocortisone, and oral prednisolone acetate, the pneumonia symptoms were well controlled. He had a history of recurrent eczema, abscesses and herpes zoster of the skin, and asthma, and he was allergic to foods including milk, eggs, and seafood. The patient had been treated with gamma globulins several times; however, the treatment had been discontinued because of a gamma globulin allergy. There was no family history of HIES.

At the age of 10 years, the patient underwent resection of masses in the gingiva and left submandibular regions. The histopathological diagnosis was chronic inflammation of the lymph node and gingival mucous tissue with eosinophil infiltration (Supplementary Material Fig. S1A, B). The gingival hyperplasia recurred after the operation, and periodontal treatment was performed for severe periodontitis. The upper lip mass and hyperplasia of the gingiva developed after the prednisolone acetate for pneumonia treatment was reduced. The symptoms gradually worsened, without obvious pain or itching.

Physical examination showed the patient had a small body size, kyphotic deformity, and left palm hyperextension of 60–70 degrees. Furthermore, the following findings were noted: coarse face and neck skin, slightly prominent forehead, a broad nasal bridge with nasal tip hypertrophy, and increased orbital distance (Fig. 1A). Oral examination showed a diffuse tumour-like lesion of the upper lip with a reddish erosive nodular surface and yellowish-white exudation, and erosive buccal mucosa and lingual papillae. The swollen gingival and palatal mucosa showed thickness with a nodular appearance and redness with pseudomembrane (Fig. 1B). Many teeth were missing, and the remaining teeth were loose to varying degrees. The mass of the lip was initially suspected to be a tumour.

Panoramic radiography revealed severely resorbed maxillary alveolar bone (Supplementary Material Fig. S1D). Computed tomography (CT) showed diffuse swelling of the whole upper lip with increased density and blurred boundaries, and enlargement of the cervical lymph nodes (Supplementary Material Fig. S1E, F). Laboratory examinations showed significantly increased IgE levels (> 5000 IU/ml), with an eosinophil percentage of 32.8%. IgM (0.11 g/l), CD4+ T cells (18.8%), and the ratio of T4 to T8 cells (0.5) were decreased, while CD8+ T cells were increased (35.8%). All examinations indicated no typical bacterial, fungal, or viral infection. Biopsy of the lip showed ulceration with epithelial hyperplasia and inflammation, and infiltration of eosinophils, neutrophils, and plasma cells (Supplementary Material Fig. S1C). Based on the comprehensive examinations, a histopathological diagnosis of chronic inflammation due to immunodeficiency was made.

Systemic therapy based on immunomodulation was administered using methotrexate tablets and oral prednisolone acetate. Symptomatic local treatment included erythromycin and clotrimazole cream for the labial lesions, gargling with povidone–iodine solution, buccal cetylpyridinium chloride tablets, and compound chamomile and lidocaine hydrochloride gel for the oral lesions. After 2 years of follow-up, the tumour-like lesion of the lip had disappeared, and the vermilion showed a pale and smooth appearance (Fig. 2A). The nodular hyperplasia of the swollen gingival and palatal mucosa was alleviated (Fig. 2B). Serum IgE levels had decreased to about 3000 IU/ml. Unfortunately, 6 months after the oral lesions had resolved, the patient died of a cerebral infection.

Discussion

HIES is a rare disease with an incidence of 1 in 500,000 to 1 in 1,000,000 individuals.[2] AR-HIES, which is caused by mutations of the *DOCK8* gene, was first reported in 2009.[3] DOCK8

deficiency is characterized by profound susceptibility to recurrent viral and bacterial infections of the skin, severe allergies, and early cancer, resulting in a higher mortality rate in childhood.[4] The clinical manifestations of DOCK8-deficient patients include an abnormal gait, eczema-like rash, facial paralysis, and central nervous system lesions.[4,5] In the patient presented here, the clinical manifestations, including severe pneumonia, eczema, cutaneous infections, and allergies, and the increased IgE and eosinophil levels, abnormal T cell count, and reduced IgM levels, indicated a typical manifestation of DOCK8 deficiency.[3,4]

The dental literature describing the oral symptoms in HIES, including orolabial ulcerations, gingivitis, and prolonged candidiasis, is limited.[2,6,7] In HIES patients, the intraoral manifestations include generalized aggressive periodontitis, keratotic patches or plaques, erythema and erosion of mucosal lesions, surface grooves of the tongue, a high arched palate with a midline fibrotic bridge, and nodular gingival enlargement.[6–8] Labial lesions manifesting as angular cheilitis, eczema-like rash, widespread papilloma, and squamous cell carcinoma have been reported.[3,9–11] Disorders of tooth eruption include a failure to shed the primary dentition, microdontia, and supernumerary teeth.[7] In the present patient, the clinical manifestations, including periodontitis and an arched palate with a hyperplastic lesion, were consistent with the previous literature. In contrast, the tumour-like lesion of the lip and the hyperplasia and erosion of the gingiva have not been reported previously.

Most AR-HIES patients show increased susceptibility to viral infections and impaired tumour surveillance.[7] Since they are at a high risk of oral malignant tumours caused by viruses, such as human papillomavirus,[6] the differential diagnosis of the lip lesion was important. Therefore, two rounds of biopsies were performed to exclude the possibility of a malignant tumour in this patient. Eosinophil infiltration was the notable histological feature in both lung and lip tissues, indicating the pathological changes of local inflammation induced by general allergic or autoimmune abnormalities. Kimura disease, angiolymphoid hyperplasia with eosinophilia, and oral Langerhans cell disease, which show similar histopathological features, should also be excluded.[12] The pathogenesis of the chronic inflammatory labial lesion is still unclear. Although no evidence of positive microbial culture was obtained, a recurrent infection might be one of the reasons.[8]

For patients with HIES, long-term immunomodulatory therapy based on glucocorticoids and immunosuppressants has shown varying success rates.[2] In the present case, steroids were used to regulate the patient's immunological status; therefore, immunomodulatory and local treatment had major therapeutic effects on the oral lesions. In some case reports, treatment with gamma globulin and interferon alpha-2b has been shown to reduce the incidence of infection.[5] Allogeneic haematopoietic stem cell transplantation has also achieved relatively positive therapeutic effects.[5]

The clinical outcomes in DOCK8-deficient patients are poor because of frequent life-threatening infections, central nervous system disorders, and malignancy.[5] Since cancers can develop in 10–36% of the young patients,[3] the patients should be monitored closely for cancer. The oral symptoms in the case presented here were well-controlled by the effective therapeutic strategy, but a serious infection led to death. Therefore, close follow-up to prevent secondary infections is necessary.

Funding

This work was supported by the National Nature and Science Foundation of China (No. 81974151).

Competing interests

None.

Ethical approval

Not required.

Patient consent

Consent was obtained.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ijom.2022.03.055.

References

[1]. Hafsi W, Yarrarapu SNS. *Job syndrome. StatPearls. Treasure Island*. FL: StatPearls Publishing; 2021.

[2]. Freeman AF, Domingo DL, Holland SM. Hyper IgE (Job's) syndrome: a primary immune deficiency with oral manifestations. *Oral Dis* 2009;**15**:2–7.

[3]. Yang J, Liu Y. Autosomal recessive hyper-IgE syndrome caused by *DOCK8* gene mutation with new clinical features: a case report. *BMC Neurol* 2021;**21**:288.

[4]. Su HC, Jing H, Angelus P, Freeman AF. Insights into immunity from clinical and basic science studies of DOCK8 immunodeficiency syndrome. *Immunol Rev* 2019;**287**:9–19.

[5]. Aydin SE, Kilic SS, Aytekin C, Kumar A, Porras O, Kainulainen L, Kostyuchenko L, Genel F, Kütükcüler N, Karaca N, Gonzalez-Granado L, Abbott J, Al-Zahrani D, Rezaei N, Baz Z, Thiel J, Ehl S, Marodi L, Orange JS, Sawalle-Belohradsky J, Keles S, Holland SM, Sanal Ö, Ayvaz DC, Tezcan I, Al-Mousa H, Alsum Z, Hawwari A, Metin A, Matthes-Martin S, Hönig M, Schulz A, Picard C, Barlogis V, Gennery A, Ifversen M, van Montfrans J, Kuijpers T, Bredius R, Dückers G, Al-Herz W, Pai SY, Geha R, Notheis G, Schwarze CP, Tavil B, Azik F, Bienemann K, Grimbacher B, Heinz V, Gaspar HB, Aydin R, Hagl B, Gathmann B, Belohradsky BH, Ochs HD, Chatila T, Renner ED, Su H, Freeman AF, Engelhardt K, Albert MH. DOCK8 deficiency: clinical and immunological phenotype and treatment options—a review of 136 patients. *J Clin Immunol* 2015;**35**:189–98.

[6]. Esposito L, Poletti L, Maspero C, Porro A, Pietrogrande MC, Pavesi P, Dellepiane RM, Farronato G. Hyper-IgE syndrome: dental implications. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;**114**:147–53.

[7]. Gerreth K, Szczawinska-Poplonyk A, Kycler Z, Adamski Z, Borysewicz-Lewicka M, Breborowicz A. Factors causing oral and skin pathological features in the hyperimmunoglobulin E syndrome patient including the environmental component: a review of the literature and own experience. *Postepy Dermatol Alergol* 2020;**37**:326–32.

[8]. Domingo DL, Freeman AF, Davis J, Puck JM, Tianxia W, Holland SM, Hart TC. Novel intraoral phenotypes in hyperimmunoglobulin-E syndrome. *Oral Dis* 2008;**14**:73–81.

[9]. James J, Thekkeveetil AK, Vadakkepurayil K. Oral manifestations of Job's syndrome in a paediatric dental patient—a case report. *J Clin Diagn Res* 2016;**10**:ZD04–5.

[10]. Akinboro AO, Onigbinde MO, Oiwoh SO, Afolayan OO, Oladeji AA. Hyper-immunoglobulin E syndrome and squamous cell carcinoma of the lower lip: a case report. *West Afr J Med* 2021; **38**:180–4.

[11]. Ozarmağan G, Didem Yazganoğlu K, Agaçfidan A. Hyper-IgE syndrome with widespread premalign oral papillomas treated with interferon alpha2b. *Acta Derm Venereol* 2005;**85**:433–5.

[12]. Koslovsky DA, Kostakis VA, Glied AN, Kelsch RD, Wiltz MJ. An unusual lesion of the tongue in a 4-year-old with Job syndrome. *J Oral Maxillofac Surg* 2013;**71**:1042–9.

Correspondence to: Department of Oral and Maxillofacial Surgery
Peking University School of Stomatology
22 Zhongguancun South Street
Beijing 100081
China.
E-mail: gyyu@263.net