

Squamous Cell Carcinoma With Hyper-IgE Syndrome: A Case Report

Ayşe S. Sasihuseyinoglu, MD,* Mustafa Yılmaz, MD,* Derya U. Altıntaş, MD,*
Dilek Dogruel, MD,* Mahir Serbeş, MD,* Aysun H. Uğuz, MD,†
and Mete Kiroğlu, MD‡

Background: Hyper-immunoglobulin E syndrome (HIES) is a rare primary immunodeficiency disease characterized by recurrent infections and elevated levels of serum immunoglobulin E, usually over 2000 IU/mL. Recurrent and chronic infection of the epidermis and squamous epithelium may also be a cause of squamous cell carcinoma (SCC). SCC is rare with HIES.

Case Report: A 17-year-old male patient who was diagnosed as HIES was admitted with purulent right ear discharge. The patient had a history of eczema starting from the age of 7 months and a history of recurrent middle ear infection starting from the age of 5. Biopsy specimens were taken from the lesion in the external auditory canal, and the lesion was reported as SCC.

Conclusion: Patients with autosomal recessive HIES are at an increased risk for infections and malignancies. SCC should be considered in the differential diagnosis of the patients presenting with recurrent middle ear infections and immunodeficiency.

Key Words: child, hyper-IgE, squamous cell carcinoma

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The hyper-immunoglobulin E syndromes (HIES) comprise a group of primary immunodeficiency disorders characterized by markedly elevated immunoglobulin (Ig)E levels, recurrent staphylococcal skin abscesses, eczema, and pulmonary infections. Most of the autosomal dominant HIES (AD-HIES) have been found to be caused by the mutations in the signal transducer and activator of transcription 3 (STAT3), whereas the dedicator of cytokines 8 (DOCK8) mutations have been identified in patients with autosomal recessive HIES (AR-HIES).¹ The patients with AR-HIES have been shown to have increased number of viral infections, more neurological symptoms, and increased risk for malignancy. Extracellular infections can occur during infancy and early childhood.²

Squamous cell carcinoma (SCC) is a malignant tumor arising from keratinocytes in the epidermis or squamous

mucosal epithelium.³ SCC can occur in the areas of skin in which previous burn or scar tissue developed, long-term nonhealing wounds are located, or in the areas that have been exposed to x-rays and chemical substances such as arsenic and petroleum. In addition, chronic and recurrent infections and prolonged depression of the immune system are also among the causes of SCC. In this report, we present a case of a 17-year-old adolescent boy with SCC and HIES.

Over the last several decades, it has become increasingly clear that the immune system plays an important role in the prevention of cancer through a process called immune surveillance.⁴ The incidence of SCC is reported to be much higher in immunosuppressed patients.⁵ Worldwide, head and neck squamous cell carcinoma (HNSCC) represents the sixth most common cancer, resulting in ~550,000 diagnoses and 300,000 deaths per year.⁶ Head and neck carcinoma is a very rare entity in the pediatric age group. SCC often arises in damaged skin or the skin that has been subjected to chronic irritation. A chronic ulcer that shows features of proliferation beyond the expected granulation process should raise the suspicion of malignant transformation.³

A CASE REPORT

The 17-year-old patient had been born weighing 3500 g at term from healthy parents who were related to each other as second-grade relatives. The patient had a history of eczema starting from the age of 7 months and a history of recurrent middle ear infection starting from the age of 5. At the age of 8, the patient presented to our clinic with pneumonia and decreased IgM level. Until that age, the patient had been hospitalized 10 times because of various complaints including respiratory tract infection and diarrhea. The patient had no family history of recurrent infection, but one of his brothers died from leukemia at the age of 9. At presentation, physical examination revealed a body weight of 19 kg (<5 p), height of 96 cm (<5 p), and diffuse erythematous, papular, and squamous lesions. Bilateral crepitant rales were detected at respiratory system examination. Otorhinolaryngological examination was normal. Peripheral blood analysis showed eosinophilia (18%; 2300/mm³) and increased eosinophilic series in the bone marrow aspiration. Moreover, IgE was elevated (200 IU/mL), IgG was normal (814 mg/dL), and IgM was decreased (13 mg/dL) for the age of the patient, and the patient had no antibody response to the Hepatitis B virus, measles, rubella, and mumps vaccines. Lymphocyte subgroups were normal, and the skin test and the fx5 test administered during admission were negative. The patient was planned for the treatment of the skin lesions and pneumonia and was followed up for immunodeficiency. Intravenous Ig and prophylaxis with trimethoprim-sulfamethoxazole was started. During the follow-up, no resolution occurred in the skin lesions, and eosinophilia developed. At the fourth year of the follow-up, CD4 T cell rate was 22.4% and Ig E was 1005 IU/mL, and the patient was found to have homozygous DOCK8 mutations. Over the subsequent 2 years, the patient did not show up for the follow-up appointments and was operated upon in

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From the Departments of *Pediatric Allergy and Immunology; †Pathology; and ‡ENT Department, School of Medicine, Cukurova University, Adana, Turkey.

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Reprints: Ayşe S. Sasihuseyinoglu, MD, School of Medicine, Balcalı Hospital, Cukurova University, 01330 Balcalı/Adana, Turkey (e-mail: ssasihuseyinoglu@yahoo.com.tr).

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an other center because of purulent right ear discharge; however, no medical records were accessed with regard to this operation. At the ninth year of follow-up, the patient presented to our clinic with purulent right ear discharge for the second time. A fistula extending from the right auricle to the posterior wall of the middle ear was detected and was treated through a consultation with the otorhinolaryngology department. After about 18 months, the patient presented to our clinic with agitation and esotropia in the right eye for the third time and was diagnosed with meningitis, mastoiditis, venous sinus thrombosis, and temporal osteomyelitis. Forty-five days after discharge, the patient presented to the otorhinolaryngology department with purulent right ear discharge. Biopsy specimens were taken from the lesion in the external auditory canal, and the lesion was reported as SCC (Fig. 1). The biopsy specimens were positive for human papillomavirus Polymerase Chain Reaction (Fig. 2). In maxillofacial and neck magnetic resonance imaging, soft tissue signals with heterogeneous contrast enhancement were detected in the right external ear canal and in the temporal bone level, extending to the pterygoid fossa, infratemporal fossa, deep neck at right side, and to the paravertebral area with the involvement of C1-C2 vertebral bone structures, causing destruction of the clivus, which extends to the left paravertebral area at the same level. No distant metastasis was observed on positron emission tomography. The patient was transferred to the pediatric oncology department for the treatment of tumoral formation. Consent to publish was obtained from the patient's parent.

DISCUSSION

HIES is often characterized by respiratory infections and skin findings including newborn rash, eczema, recurrent skin abscesses, and ear, sinus, and lung infections that result in the formation of cavitary lesions in the lungs (pneumatoceles). AR-HIES with DOCK8 deficiency is particularly common in the regions of the world with high consanguinity rates (intermarriage among close relatives), wherein its occurrence may exceed that of AD-HIES. However, patients with AR-HIES are distinguished from those with AD-HIES by the occurrence of severe and recurrent viral infections caused by pathogens such as *Herpes simplex*, *Herpes zoster*, and *Molluscum contagiosum*. Moreover, patients with AR-HIES are also susceptible to allergic and autoimmune manifestations including food allergy, hemolytic anemia (due to red blood cell destruction by antibodies), and vasculitis (inflammation within blood vessels). Patients with AR-HIES also have a high frequency of neurological complications, including encephalitis (brain inflammation) and vascular brain lesions. Patients with

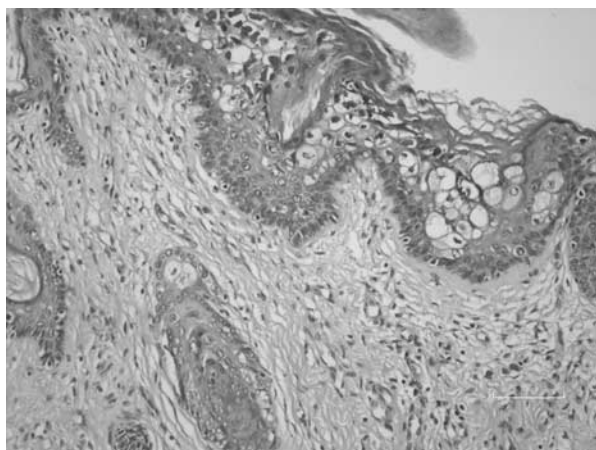


FIGURE 1. Epidermodysplasia verruciformis focus includes large pale keratinocytes, perinuclear halo and keratohyaline granules (HE, x400).

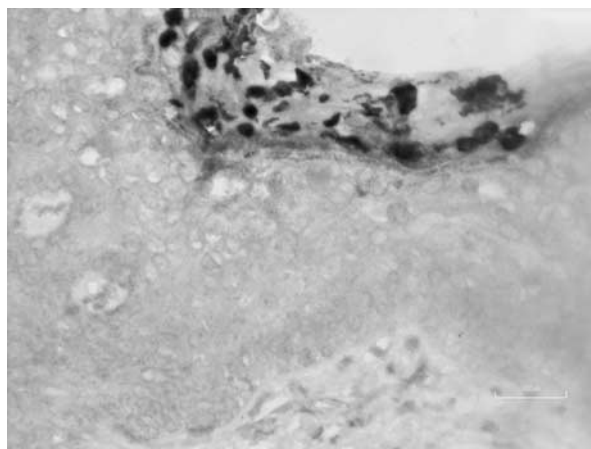


FIGURE 2. HPV positivity in koilocytic cells in epidermodysplasia verruciformis focus (Immunohistochemistry, x400).

DOCK8 deficiency have more symptomatic neurological diseases than those with STAT3 deficiency. Neurological manifestations may range from limited involvement such as in facial paralysis to more severe manifestations such as in hemiplegia and encephalitis. Both AD-HIES and AR-HIES patients are at increased risk for malignancies, especially lymphomas. Moreover, patients with DOCK8 deficiency are susceptible to papilloma virus-induced SCC and to lymphomas. Aydın et al⁷ conducted a study on 136 patients with DOCK8 mutations and detected various diseases in 23 patients, of which 39% were epithelial malignancies.

Wiser et al⁸ postulated that the HNSCCs in their study mostly originated from the scalp and the ear. In another study in which 12 pediatric HNSCC cases were investigated, the mean age was 17 (range, 8 to 12) years and the male/female ratio was found to be 11/1.⁹ In the same study, 17% of the tumors were located in the soft palate, 17% in the gingiva, 17% in the supraglottic larynx, and the rest were located in the hard palate, buccal mucosa, or the floor of the mouth. In contrast, Yin et al¹⁰ did not find any typical initial complaint in 95 adult patients with SCC originating from the outer and middle ear, and 12.6% of the patients had a history of recurrent otitis external or chronic otitis media.

The choice of SCC treatment modality depends on the degree of differentiation of the tumor and the presence or absence of metastasis. The size, shape, location of the tumor, and the predisposing factors should also be considered. In case of a localized, well-differentiated tumor with no evidence of metastasis, the primary goal should be to achieve complete eradication of the lesion. In the case of a poorly differentiated, recurrent tumor, or the presence of lymph node metastasis, palliative treatment may be considered if complete eradication is deemed impossible. The modalities available for consideration include excision surgery, Mohs surgery, cryosurgery, electrosurgery, and radiation therapy.¹¹

CONCLUSIONS

Patients with AR-HIES are at increased risk for infections and malignancies. Chronic and recurrent infections and prolonged depression of the immune system are among the causes of SCC. The case presented in this study highlights that SCC should be considered in the differential diagnosis of the patients presenting with recurrent middle ear infections.

REFERENCES

1. Yong PF, Freeman AF, Engelhardt KR, et al. An update on the hyper-IgE syndromes. *Arthritis Res Ther*. 2012;14:228. Doi:10.1186/ar4069.
2. Eberting CL, Davis J, Puck JM, et al. Dermatitis and the newborn rash of hype- Ig E syndrome. *Arch Dermatol*. 2004; 140:119–125.
3. Neel, VA, Sober, AJ. Tumors arising from the epidermis victor A. In: Kufe DW, Pollock RE, Weichselbaum RR, Bast RC, Gansler TS, Holland JF, Frei E, III, eds. *Holland-Frei Cancer Medicine*, 6th ed. Hamilton, ON: BC Decker; 2003:213–218.
4. Dunn GP, Bruce AT, Ikeda H, et al. Cancer immune editing: from immunosurveillance to tumor escape. *Nat Immunol*. 2002; 3:991–998.
5. Rowe DE, Carroll RJ, Day CL. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip: implications for treatment modality selection. *J Am Acad Dermatol*. 1992;26:976.
6. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin*. 2011;61:69–90.
7. Aydın SE, Kilic SS, Aytekin C, et al. DOCK8 deficiency: clinical and immunological pheno type and treatment options-a review of 136 patients. *J Clin Immunol*. 2015;35:189–198.
8. Wiser I, Scope A, Azriel D, et al. Head and neck cutaneous squamous cell carcinoma clinicopathological risk factors according to age and gender: a population-based study. *Isr Med Assoc J*. 2016;18:275–278.
9. Bhanuprasad V, Mallick S, Bhasker S, et al. Pediatric head and neck squamous cell carcinoma: report of 12 cases and illustrated review of literature. *J Pediatr Otorhinolaryngol*. 2015;79:1279–1282.
10. Yin M, Ishikawa K, Honda K, et al. Analysis of 95 cases of squamous cell carcinoma of the external and middle ear. *Auris Nasus Larynx*. 2006;33:251–257.
11. Hruza GJ. Mohs micrographic surgery. *Otolaryngol Clin North Am*. 1990;23:845.