A Novel γ -Secretase Gene Mutation in a Japanese Family with Hidradenitis Suppurativa

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Introduction

Hidradenitis suppurativa (HS) is a chronic relapsing inflammatory skin disease that presents with painful nodules, abscesses, and sinus in apocrine gland-bearing area. Familial HS (OMIM # 142690) usually shows an autosomal dominant inheritance pattern and appears to be genetically heterogeneous¹. Mutations in γ -secretase genes *NCSTN*, *PSENEN* and *PSEN1* have been reported in a small number of familial and sporadic cases². We found a novel heterozygous *NCSTN* mutation c.1285C>T (p.R429del) in a Japanese familial HS patient with secondary squamous cell carcinoma (SCC).

Case report

A 36-year-old male presented with relapsing nodules on his face, body, limbs since he was 15 years old. When he was 20 years old, abscesses were seen on his hip. He visited our department in June 2008. His maternal grandmother, uncle, mother and younger brother also have similar symptoms (Fig1). On his first visit, various-sized multiple nodules and pustules were distributed to the body and limbs (Fig2, Fig3-A). He underwent multiple surgeries and took several kinds of antibiotics. The various treatments were palliative but not sufficiently effective. Six years later from his first visit, a tumor on his right hip enlarged (Fig3-B), and a diagnosis of SCC was made histopathologically (Fig4). Despite the treatment with chemotherapy, radiation, and surgical excision, the tumor relapsed and metastasized to the sacral bone (Fig3-C) and inguinal lymph nodes. He died in September 2016.

Fig 1) Family tree

Fig 2) Clinical photograph (first visit)

Fig 3) Clinical course

Fig 4) Histopathology

Proliferation of atypical keratinocytes with foci of keratinization are seen in epidermis and dermis. Red arrow (→) shows a horn pearl.

Diagnosis:
Squamous cell carcinoma

Objective

To identify mutations in the gene encoding γ -secretase in this Japanese familial HS

Methods

Peripheral blood was obtained from proband and his younger brother. Genomic DNA was extracted from their peripheral blood, using QIAamp DNA Blood Maxi Kit (Qiagen, Germantown, MD, U.S.A.), for polymerase chain reaction (PCR) amplification of *NCSTN*, *PSENEN* and *PSEN1*. PCR was performed by using the exon-flanking intronic primer and the PCR products were purified for sequencing analysis done by Greiner bio-one Japan (Tokyo, Japan)

Results

Sequencing analysis detected a single nucleotide mutation c.1285c>t in *NCSTN* gene (Fig 5). The mutation is nonsense mutation, resulting in the truncation of NCSTN protein at codon 429 (Fig 6). Electrogram shows the nucleotide mutation was heterozygous of T and C (Fig 7). Proband's younger brother has also the same heterozygous *NCSTN* mutation (Fig 8). R429 is located at the extracellular domain of *NCSTN*³ (Fig9).

Fig 5) #NCSTN_CDS W/T 1261 CCTCTCCACCATCTTCCTGCGGATTTCTTCGAG
#NCSTN_CDS_mut 1261 CCTCTCCACCATCTTCCTGCGGATTTCTTCGAG
1285

Fig 6) #NCSTN_CDS_1 W/T 421 FLPPSSIQRFIRARNISGVVLADI
#NCSTN_CDS_mut_1 421 FLPPSSIQRFIRARNISGVVLADI
429

Fig 7) Proband

Fig 8) Proband's younger brother

Fig 9)

Discussions

Since the mutation found in the present cases make huge truncation of NCSTN protein, it could result in severe dysfunction of γ -secretase. γ -secretase is known to cleave the intracellular domain of Notch. Notch signaling plays a pivotal role in hair follicle differentiation, in the maintenance of the epidermal barrier function, and as an epidermal tumor suppressor. Impaired Notch signaling may result in aberrant T-cell function with deficient IL-22 secretion, auto-inflammatory Th17-driven immune reactions, NK cells reduction and a risk of SCC⁴.

Conclusions

- ① Japanese familial HS complicated with secondary SCC carrying a novel γ -secretase gene mutation.
- ② This finding suggests the possibility that γ -secretase mutation may be associated with the occurrence of malignant tumor in HS patients.

References

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