An 8-year-old boy presented with three painless nodules on the abdomen, back, and left arm for the duration of 1 year (Figure 1). The skin examination showed three 10 mm × 6 mm skin-colored, well-circumscribed, dome-shaped nodules on the abdomen, lower back, and left antecubital fossa. The patient had strabismus and left ptosis for 2 years, and maculopathy was noted for 1 month. He had no hearing loss or tinnitus. Tracing back his medical history, he had relative attention deficit, poor memory, lethargy, and coordination disorder, especially in fine movement for 3 years. There was no family history. Skin biopsy was done over abdomen (Figure 1A). Microscopic finding showed multiple encapsulated cellular nodules consisting of spindle cell with Verocay bodies, and plexiform schwannoma was impressed. Meanwhile, gene analysis was performed. A heterozygous nonsense mutation (1219C>T, Q407X) was detected in Exon 12 by direct DNA sequencing (Figure 2A). The father and mother showed normal sequence (Figure 2B). Auditory brainstem response showed normal brainstem auditory evoked potential. The initial brain magnetic resonance imaging (MRI) showed a tumor within left internal acoustic canal favoring vestibular schwannoma and a right cerebellopontine angle tumor favoring trigeminal schwannoma (Figure 3).

Figure 1 Skin-colored, well-circumscribed, dome-shaped nodules about 10 mm × 6 mm on the (A) abdomen and (B) lower back of the 8-year-old boy.

Figure 2 (A) Automated DNA sequencing of NF2 gene reveals a single nucleotide nonsense mutation (1219C>T, Q407X) in Exon 12. (B) Normal sequence from control and parents.
diagnosis

de novo mutation of neurofibromatosis type II (NF2).

discussion

cyberknife stereotactic radiotherapy with 2100 cGy in three fractions targeting the former and 2250 cGy in five fractions targeting the latter were done in order. The two tumors seemed to be stationary for about 2 years. However, new enhancing tumors on the brain MRI was noted over left oculomotor and facial nerves, and right vestibular and lower cranial nerves afterward. Further follow-up was suggested.

NF2 (OMIM 101000) is an inherited autosomal dominant, multiple neoplasia syndrome characterized by tumors of the eighth cranial nerve (usually bilateral), meningiomas of the brain, and schwannomas of the dorsal roots of the spinal cord. NF2 is caused by mutations in NF2 tumor suppressor gene, which contains 17 exons on chromosome 22q12. Merlin (moesin-ezrin-radixin-like protein) or schwannomin, which is encoded by the Exon 1–15 and 17 of NF2 gene and has 595 amino acid residues, contains three domains in order: a trilobed amino-terminal FERM (four-point-one, ezrin, radixin, moesin) domain, an α-helical domain, and a carboxy-terminal domain. The FERM domain connects to carboxy-terminal domain when the serine-518 on the latter is phosphorylated, and the coiling of merlin at this active stage enables the tumor suppression activity.1 Mutation of NF2 gene results in the unique spectrum of tumor formation, such as schwannomas and other lesions in the nervous system, eyes, and skin.

According to the study of Selvanathan et al.,2 there are correlations between the genotypes and phenotypes in NF2. Patients with nonsense or frameshift mutations are associated with severer presentation. They are younger at diagnosis; become symptomatic earlier; more likely to have meningiomas, spinal tumors, and nonvestibular cranial nerve tumors; and have more cutaneous lesions.2 Splice site mutations are related to both mild and severe disease and may be milder if occurring in the 3′ half of the gene. Missense mutations are usually mild, often causing the mildest form of NF2.3 Besides, patients with truncating mutations were significantly more likely to develop symptoms before 20 years of age and develop at least two symptomatic central nervous system tumors in addition to vestibular schwannoma before 30 years of age.4 NF2 was first described in a deaf patient with tumors in the skull, dura mater, and brain in 1822. It was considered to be related to the other types of neurofibromatosis, such as neurofibromatosis type 1 (NF1) and schwannomatosis.5 However, not until 1987 did the localization of NF2 and NF1 on chromosome 22 and 17q11 respectively separate them as different entities. In clinical manifestation, schwannomas are common in NF2, whereas neurofibromas are common in NF1. Schwannomatosis was further discriminated from NF2 by its definition as multiple schwannomas without vestibular schwannomas that are diagnostic of NF2 and its mutation of INI1 (SMARCB1) gene on chromosome 22q11.3

The clinical diagnosis is made, according to Manchester criteria, by fulfilling either one of the four conditions, including (1) bilateral vestibular schwannomas; (2) first-degree relative with NF2 and either having unilateral vestibular schwannoma or any two of the following: meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities; (3) unilateral vestibular schwannoma and any two of the following: meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular lenticular opacities; (4) multiple meningiomas and unilateral vestibular schwannoma or any two of the following: glioma, neurofibroma, schwannoma, and cataract.5 Evaluations after initial diagnosis must include: brain MRI, hearing evaluation (auditory brainstem response), ophthalmologic evaluation, and cutaneous examination.3 The treatment mainly focuses on the manifestations of each system. Surgery and stereotactic radiotherapy are the choices for vestibular schwannoma.

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Yi-An Chen, Hung-Chien Lin, Sheau-Chiou Chao*
Department of Dermatology, National Cheng Kung University Hospital and College of Medicine, National Cheng Kung University, Tainan, Taiwan
*Corresponding author. Department of Dermatology, National Cheng Kung University Hospital and College of Medicine, National Cheng Kung University, No. 138, Sheng-Li Road, Tainan, Taiwan
E-mail address: joly@mail.ncku.edu.tw (S.-C. Chao)

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