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Choroid plexus papilloma in a girl with hypomelanosis of Ito

Case report

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The authors report a case of choroid plexus papilloma in a girl with hypomelanosis of Ito, and they review the literature in brief. Hypomelanosis of Ito is a rare neurocutaneous syndrome characterized by cutaneous hypopigmented whorls, streaks, and patches along lines of Blaschko. Most patients exhibit CNS manifestations, including psychomotor retardation, seizures, hypotonia, and ataxia. A 6-year-old girl with hypomelanosis of Ito was referred to the authors' hospital with bilateral tumors in the lateral ventricles. The right lateral ventricle tumor was surgically removed. Immunohistochemical investigations revealed the tumor to be a choroid plexus papilloma (WHO Grade I). A chromosomal investigation revealed that the tumor tissue demonstrated a large loss of heterozygosity at chromosome 10. The case reported here serves as a reminder that de novo brain tumors may arise in patients with chromosomal mosaicism.
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Key Words • **neurocutaneous disorder** • **chromosome** • **papilloma** • **choroid plexus** • **PTEN protein** • **hypomelanosis of Ito** • **oncology**

Hypomelanosis of Ito is the third most frequently occurring neurocutaneous disease, exceeded only by neurofibromatosis Type 1 and tuberous sclerosis, with an incidence of about 1 per 600–700 patients referred to a pediatric neurology service.[6] Various chromosomal mosaics and X-autosome balanced translocations have been reported for most autosomal or sex chromosomes.[8] Hypomelanosis of Ito is characterized by uni- or bilateral macular cutaneous hypopigmented whorls, streaks, and patches along the lines of Blaschko, and it manifests during childhood.[10,15] Most patients with HI commonly have extracutaneous manifestations of the disease, including psychomotor retardation, autistic behavior, seizures, hypotonia, and macrocephaly.[6] White matter alterations, migrational abnormalities, hemispheric asymmetry, diffuse cerebral atrophy, brainstem atrophy, cerebellar atrophy, cerebellar hypoplasia, and agenesis or dysplasia of the corpus callosum, are often revealed on neuroimages in patients with HI.[6] Musculoskeletal manifestations such as kyphoscoliosis, hypertelorism, body hemiatrophy, spina bifida, and syndactyly, and ocular system manifestations such as strabismus, myopia, chorioretinal atrophy, nystagmus, and microphthalmia are also characteristic features.[8] In addition, patients with HI sometimes manifest tumors; thus far, 4 cases of brain tumors associated with HI have been documented (Table 1).[9,10,14,15] We report the second case of HI associated with choroid plexus papilloma; the chromosomal abnormality found in the present case differed from that in the first reported case.[9,15]

Abbreviation used in this paper: HI = hypomelanosis of Ito.

Case Report

History and Examination. This girl was born after an uneventful pregnancy at 38 weeks of gestation with a birth weight of 3886 g and a normal head circumference. Skin hypopigmentation along the lines of Blaschko (Fig. 1A and B) and bilateral chorioretinal atrophy were noted at the age of 9 months. The patient showed developmen-

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

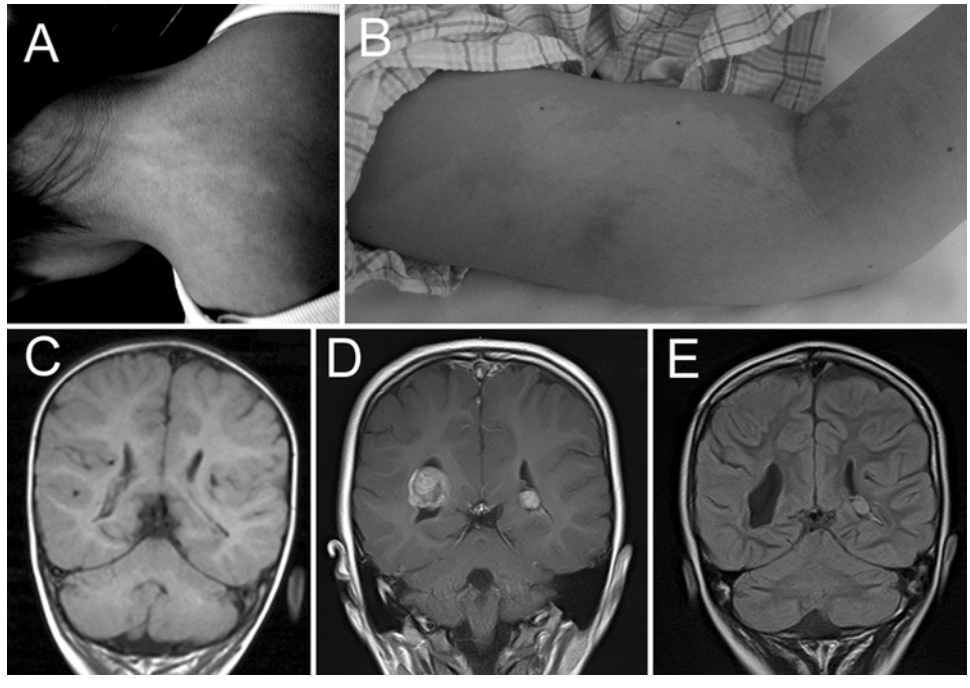

Fig. 1. Features of the patient's skin and brain MRI studies. **A and B:** Sharply demarcated, hypopigmented streaks are seen in a linear pattern on the neck and right arm. **C:** Coronal T1-weighted image obtained 4 years prior to the operation, demonstrating the absence of tumor. **D:** Coronal Gd-enhanced T1-weighted image showing bilateral intraventricular tumors. **E:** Coronal FLAIR image demonstrating total resection of the left ventricle tumor and no tumor recurrence. The right ventricle tumor remains unchanged.

tal delays and severe mental retardation; she was unable to stand up until she was 18 months old, and her speech was severely impaired. There was no family history of neuropsychomotor retardation, seizures, tumors, or pigmentation anomalies of the skin. At 6 years of age, she experienced complex partial seizures and was admitted to our hospital for examination of the brain lesions found on MRI.

The MRI studies showed bilateral lesions in the lateral ventricles that had not been apparent 4 years earlier (Fig. 1C and D). There was no evidence of white matter alterations, brain atrophy or hypoplasia, hemispheric asymmetry, gray matter heterotopias, polymicrogyria and agenesis, or dysplasia of the corpus callosum. Magnetic resonance angiography and digital subtraction angiography did not reveal vascular anomalies. On admission, the patient was alert and had no deficits in her cranial nerves. Although her muscle tonus was slightly hypotonic, no motor weakness was noted. Her sensory system seemed intact, although precise examinations of the sensory system were impossible due to her severe mental retardation manifested, in part, through her minimal use of words and difficulty in communicating. Electroencephalography revealed moderate alterations, mainly left parietal paroxysmal disturbances. On the basis of these clinical manifestations, her condition was diagnosed as HI.

Operation and Postoperative Course. Resection of the right lateral ventricle lesion was performed via a transcortical approach. At the 40-month follow-up examination, there was no relapse of the tumor, and the tumor on the contralateral side was unchanged (Fig. 1E). The patient's clinical status remained unchanged.

Diagnosis and Chromosomal Analyses of the Tumor. Pathological examination revealed that the tumor was a choroid plexus papilloma (WHO Grade I) (Fig. 2A). Immunohistochemical analysis revealed that the expression of tumor suppressor PTEN was negative in the tumor cells (Fig. 2B). The chromosomal analyses of the peripheral blood lymphocytes were normal, whereas the tumor cells revealed a large loss of heterozygosity: 46,XX,del(10)(p?;q?) (Fig. 2C and D).

Discussion

Chromosomal analysis of the tumor cells in the present case showed a large loss of heterozygosity on 10p and 10q. Immunohistochemical analysis revealed that the tumor cells were PTEN negative. In a previously reported case of chromosome 10–associated HI, the patient presented with delayed neuropsychomotor development, abnormal electroencephalogram, and an arachnoid cyst in the temporal region.[1] The patient showed chromosome mosaicism at 46,XY/46XY,del(10)(q.22.2–24.2), and this locus indicated inclusion of the *PTEN* (10q23.31) as well as pigmentary genes such as those associated with *HPS1* (10q24.2).[12] The mutation of *PTEN* is known to have a predilection for the development of tumors as well as mental retardation, ataxia, seizures, and macrocephaly through changes in neuronal morphogenesis.[2,13] Bannayan-Riley-Ruvalcaba syndrome is a well-known *PTEN* deficiency–

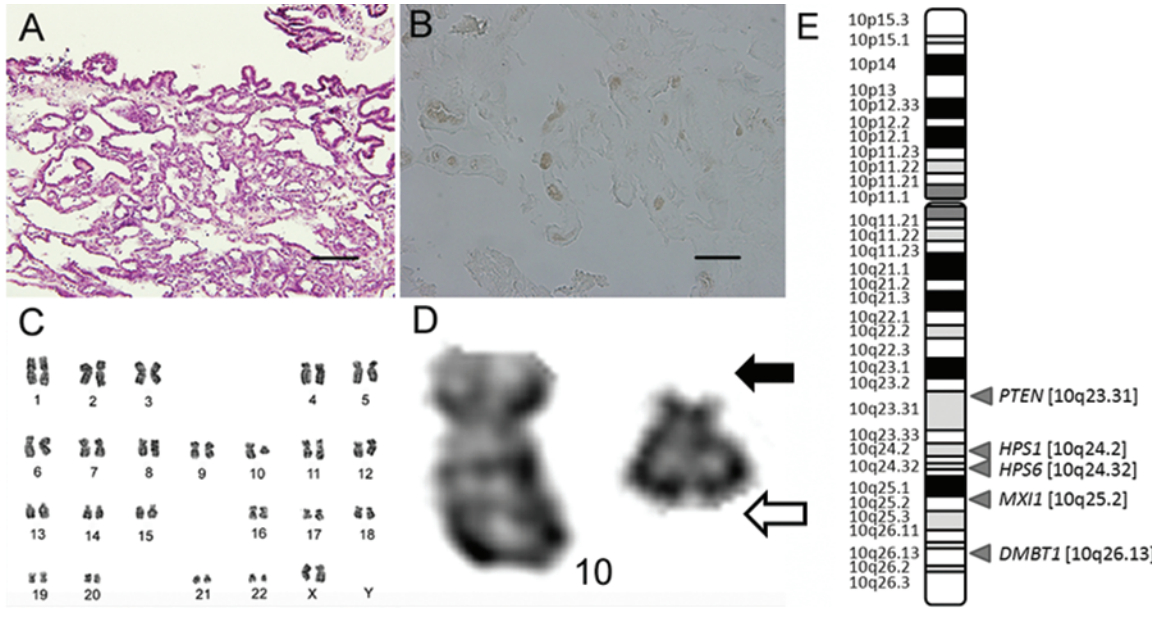

Fig. 2. Histological, immunohistological staining, and karyotype of the tumor. **A:** A well-maintained papillary structure and single-layered epithelium are seen. There are no mitotic cells (H & E). **B:** Immunohistochemical staining demonstrating the absence of PTEN expression in tumor cells. Note the vascular structures are stained positive with anti-PTEN antibody. **C:** Karyotype from the patient's plexus papilloma showing a large loss of heterozygosity on chromosome 10. **D:** Enlarged view of chromosome 10. Large loss of heterozygosity is found on 10p *(black arrow)* and on 10q *(white arrow)*. **E:** Schematic drawing of chromosome 10 with previously known tumor suppressor genes (*PTEN*, *MXI1*, and *DMBT1*) and pigmentary genes (*HPS1* and *HPS6*) shown concomitantly. Bar = 100 μm (A) and 20 μm (B).

associated childhood syndrome.[4] Clinical manifestation of Bannayan-Riley-Ruvalcaba syndrome is characterized by macrocephaly, intestinal hamartomatous polyps, lipomas, pigmented maculae of the glans penis, downward slanting of the eyes, hypotonia, seizures, developmental delays, and mental retardation. These clinical manifestations also have some clinical overlap with those described by Almeida et al.[1] and in the present case.

With respect to tumorigenesis, Rickert et al.[7] reported that the most frequently found chromosomal deletions among the 34 choroid plexus papillomas were loss of heterozygosity of 10q (56%) and 10p (47%). The tumor suppressor genes *PTEN*, *MXI1* (10q25.2), and *DMBT1* (10q26.13) are known to be located on 10q (Fig. 2E). Although identification of the responsible gene for the present case would be difficult due to the large deletion, *PTEN* could be a candidate because of its many functions.[2,13]

The previously reported CNS tumors in patients with HI are summarized in Table 1; 2 benign[9,15] and 2 malignant cases[10,14] have been reported. Among them, 2 cases exhibited chromosomal abnormalities.[9,15] In the remaining cases, the karyotype was normal in one case[10] and the chromosomal analysis was not available in another case.[14] One patient with HI and choroid plexus papilloma had a translocation at (X;17)(q13;p13).[9,15] The authors postulated that *FMR1L2* may play an important role in the pathogenesis of mental retardation and speculated that the 17p tumor-related locus (17p13.3) might activate *p53*.

TABLE 1: Central nervous system tumors associated with HI*

Authors & Year	Age (yrs), Sex	CNS Tumor Type; Tumor Karyotype	Presentation	Other Associated Features	Treatments for Tumors	Outcome
Steichen-Gersdorf et al., 1993, & Zajac et al., 1997	5, F	CPP (WHO Grade I); 46,XX,t(X;17)(q12;p13)	gross motor retardation	macrocephaly, nevoid hypopigmentation of retina	resection	NA
Steiner et al., 1996	9, M	medulloblastoma; 46,XY (normal)	deafness	hydrocephalus	resection & chemo	death at age 11 yrs
Xu et al., 2000	1, M	meningeal rhabdomyosarcoma; NA	regression of language, flaccid paresis of upper extremities, seizures, Bell palsy	hydrocephalus	biopsy, RT & chemo, VPS	improvement 1 mo after RT
present case	6, F	CPP (WHO Grade I); 46,XX,del(10)(p?;q?)	psychomotor retardation, seizures, hypotonia	chorioretinal atrophy	resection	no change at 40 mos postsurgery

* chemo = chemotherapy; CPP = choroid plexus papilloma; NA = not available; RT = radiation therapy; VPS = ventriculoperitoneal shunt.

Interestingly, several studies have suggested that p53 and PTEN functionally affect each other.[2]

Although the pathogenesis of HI is unknown due to the many different karyotypic abnormalities involving different chromosomes,[11] the described chromosomal varieties indicate that HI is a phenotype rather than a syndrome. In other words, HI is a cutaneous sign of mosaicism.[5,12] Thus, irrespective of the loci of chromosomal abnormalities, it is important to note that de novo brain tumors may arise in patients with mosaic forms of skin disorders because they are manifestations of chromosomal imbalances.[3] Additional experience with a greater number of patients is required to support this notion.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Morigaki. Acquisition of data: Morigaki, Pooh, Shouno, Taniguchi. Analysis and interpretation of data: Morigaki, Pooh, Endo, Taniguchi. Drafting the article: Morigaki. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Morigaki. Administrative/technical/material support: Taniguchi.

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