Phylloid Hypomelanosis and Mosaic Partial Trisomy 13

Two Cases That Provide Further Evidence of a Distinct Clinicogenetic Entity

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Background: Phylloid hypomelanosis is a rare neurocutaneous syndrome characterized by a pattern of hypopigmentation consisting of leaflike or oblong macules reminiscent of floral ornaments. Associated extracutaneous anomalies include cerebral, ocular, and skeletal defects. Recently it has been suggested that this phenotype originates from mosaic partial or complete trisomy 13. We report clinical and cytogenetic data for 2 cases.

Observations: A bizarre pattern of multiple leaflike macules was noted in 2 girls with mental deficiency. In patient 1, additional anomalies included syndactyly, clinodactyly, trichomegaly of the eyelashes, low frontal hairline, and several pale pink telangiectatic macules. In patient 2, epileptic seizures, dental malposition, oligodontia, preauricular fistulas, scoliosis, tethered cord, and syringomyelia were noted. A diagnosis of phylloid hypomelanosis was made in both patients. In both patients, blood lymphocytes showed a normal karyotype 46,XX; however, fibroblasts derived from lesional skin demonstrated tetrasomy of chromosome 13q21-qter in patient 1 and trisomy of 13q22-qter in patient 2.

Conclusions: These 2 cases lend further support to the concept that phylloid hypomelanosis is a distinct clinicogenetic entity that should no longer be confused with pigmentary mosaicism of the Ito type. From a comparison of our cytogenetic findings with those documented in previous articles, we infer that phylloid hypomelanosis is most likely related to the 13q region.


In 1993, the phylloid pattern was delineated as a peculiar type of pigmentary mosaicism characterized by macules reminiscent of floral ornaments in the form of round or oval spots, patches resembling the asymmetric leaves of a begonia, and oblong lesions.1 Subsequently, the term phylloid hypomelanosis was suggested to define a distinct syndrome consisting of achromic phylloid skin lesions in combination with extracutaneous anomalies such as mental retardation, agenesis of the corpus callosum, conductive hearing loss, coloboma, and various skeletal defects.2 Because this phenotype seemed to be consistently associated with mosaic trisomy 13, it was proposed to be a new etiologically defined syndrome.3 We report 2 additional cases providing further evidence that this particular phenotype is a distinct entity.

REPORT OF CASES

CASE 1

An 8-year-old girl had hypopigmented macules that were noted during the first year of life. At school, she had learning difficulties. Her parents were healthy and nonconsanguineous; her brother was also healthy.

Physical examination revealed a bizarre pattern of multiple leaflike macules involving the trunk and limbs (Figure). Rather thick eyebrows, long eyelashes, and a low frontal hairline were noted. Several pale pink telangiectatic lesions involved the midfacial area, neck, and right lumbar region. In addition, bilateral syndactyly of the second and third toes and bilateral clinodactyly of the fifth finger were present. Neurologic and ophthalmologic examinations yielded no abnormalities.

Cytogenetic analysis of peripheral blood lymphocytes showed a normal karyotype 46,XX. Fibroblasts derived from skin, however, showed mosaicism of karyotypes 47,XX,+der(13)(13)(q21-qter)/46,XX. The aberrant karyotype was found in 26 of 32 cells derived from light skin and in 37 of 50 cells derived from dark skin. By application of the fluorescent in situ hybridization technique, the derivative chromosome was categorized as 13 ish tel 13q.

CASE 2

A 15-year-old girl with mental deficiency had numerous depigmented macules...
present since birth. A sacral fistula was also noted at birth. Her parents were healthy and nonconsanguineous. She had 1 brother and 1 sister who were both healthy. The patient was receiving anticonvulsive treatment because of absence seizures that had first occurred at the age of 2 years. At the age of 10 years, a diagnosis of tethered cord was made and syringomyelia of the lumbar region was noted. At age 14 years, scoliosis was surgically corrected.

Physical examination revealed a phylloid pattern of multiple achromic macules on the trunk and limbs. Bilateral preauricular fistulas were present. Her teeth showed malposition, and 3 molars were absent. In addition, multiple subcutaneous abscess lesions and fistulas involved the sacral area, buttocks, and proximal part of the thighs. A salmon patch was noted in the sacral region.

Cytogenetic analysis of blood lymphocytes showed a normal karyotype 46,XX. In fibroblasts derived from lesional skin, however, a karyotype 47,XX+mar. rev. ish enh(13) (q22qter) was found in all cells examined (n=20). This result was obtained with the fluorescent in situ hybridization technique and was subsequently confirmed with high-resolution comparative genomic hybridization.

**COMMENT**

When phylloid hypomelanosis was first proposed as a distinct syndrome, 6 pertinent articles were reviewed. Our 2 cases lend further support to the idea that this is a separate phenotype that usually heralds mosaic trisomy 13 that may be partial, as in our 2 patients, or, more rarely, complete. From a comparison of all of these cases, we conclude that phylloid hypomelanosis is most likely related to the 13q region.

The most important differential diagnosis is pigmentary mosaicism of the Ito type. This Blaschko line hypopigmentation may be associated with extracutaneous anomalies. The nonspecific term hypomelanosis of Ito gives the wrong impression of a nosologic entity. Pigmentary mosaicism of the Ito type is a clinical umbrella term that includes many different states of mosaicism. Only some of these mosaic disorders are recognizable at the cytogenetic level.

The ongoing confusion that is caused by the term hypomelanosis of Ito is illustrated by the following 2 case reports. In 2001, Kaya et al reported a typical case of phylloid hypomelanosis under the designation hypomelanosis of Ito. However, no cytogenetic analysis was performed in this patient. In 2002, Yakinci et al described a boy with “hypomelanosis of Ito with trisomy 13 mosaicism.” The authors erroneously believed that this was “the first case reported in the literature showing an association between phylloid pigmentary pattern of hypomelanosis of Ito and trisomy 13 mosaicism.” From the clinical photographs, we have the impression that the leaf-shaped patches on their patient were hyperpigmented rather than hypopigmented, which is why we hesitate to accept this case as an example of phylloid hypomelanosis.

Our 2 cases show the characteristic phenotypic and cytogenetic features of phylloid hypomelanosis and further expand the clinical spectrum of this syndrome. In patient 1, typical defects such as mental deficiency, syndactyly, and clinodactyly were noted. Abnormal hair growth in the form of thick eyebrows, long eyelashes, and low frontal hairline can be considered additional features of this syndrome, as is the presence of pale pink telangiectatic macules that are commonly observed in both mosaic and nonmosaic trisomy 13. In patient 2, epileptic seizures and mental deficiency are typical features of the syndrome, and dental malposition, oligodontia, preauricular fistulas, scoliosis, and tethered cord also are part of the clinical spectrum of the disorder. However, it is unclear whether the inflammatory lesions reminiscent of hidradenitis suppurativa are nosologically related to the phenotype. Our 2 patients were girls, and all typical cases of phylloid hypomelanosis reflecting mosaic trisomy 13 reported to date have been in girls. We are unable to explain this remarkable sex ratio of 8:0.

In principle, it would have been worthwhile to examine biopsy specimens from lesional skin for the presence and function of melanocytes. In our patients, however, the parents did not give permission to obtain such additional biopsy tissue.

Mosaic trisomy 13 is far less frequently observed than nonmosaic trisomy 13 (Patau syndrome), which is a se-
vere birth defect characterized by microcephaly, serious central nervous system anomalies, congenital heart defects, holoprosencephaly, cleft lip or palate, microphthalmia, polydactyly, scalp defects, and numerous other developmental anomalies. Affected children usually die within the first year of life. Nothing is known about pigmentary disturbances in nonmosaic trisomy 13.

In conclusion, our 2 cases provide additional evidence that phylloid hypomelanosis comprises multiple birth defects and a distinct new entity. Clinicians should bear this differential diagnosis in mind when seeing a patient with so-called hypomelanosis of Ito. The nonspecific term hypomelanosis of Ito refers to a cutaneous symptom present in numerous different states of mosaicism, which is why no particular cytogenetic or molecular diagnosis can be predicted. Conversely, when a phylloid pattern is present, we should be able to interpret these signs and foretell the presence of a specific chromosomal abnormality in the form of mosaic trisomy 13.

Exceptional cases of phylloid hypomelanosis in which no trisomy 13 can be found also may occur. The percentage of such cases is unknown; however, at this time, we predict that, in most patients exhibiting phylloid achromic macules in combination with extracutaneous defects, partial or complete mosaic trisomy 13 will be present.

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