Hypomelanosis of Ito in Two Infants: A Case Series with Literature Review

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Abstract

Hypomelanosis of Ito is an uncommon condition representing pigmentary and chromosomal mosaicism. Characteristic findings include whorls and streaks of hypopigmentation involving some or all of the skin surface and generally following the lines of Blaschko. Associated systemic findings include orthopedic, neurologic, ocular and dental anomalies, but the severity of extracutaneous involvement varies greatly from cases to case. We report two cases of hypomelanosis of Ito: a 4-month-old male infant with extensive cutaneous involvement, associated joint contractures and presumed neurologic developmental delay; and a 3-month-old male with limited skin involvement and no apparent systemic involvement.

Introduction

Pigmentary disorders are common in infants and children, often causing emotional distress to parents and providers. Hypomelanosis of Ito is an uncommon condition representing somatic mosaicism, with hypopigmented patches and streaks following the lines of Blaschko. Associated systemic findings range from none to severe systemic effects. The diagnosis is clinical, based on history and physical examination, and subsequent workup is based on associated findings. Currently, there is no treatment for cutaneous manifestations.

Case Reports

Case 1

A 4-month-old male Hispanic infant presented to our clinic with a primary concern of unusual pigmentation covering the child's entire body. The mother stated that when the infant was born, she noticed mild pigmentation changes, but by two weeks of age the pigmentation was very noticeable. The child had been diagnosed with bilateral sensorineural hearing loss, plantar flexion contractures of the feet bilaterally, ankle contractures and flexion contractures of the fingers. His pediatrician was concerned for developmental delay based on poor head control and delayed motor skills. The gestational period was uneventful, with the patient being born at term with a normal vaginal delivery. Family history was reviewed and not contributory.

On examination, the patient had whorls and streaks of hypopigmented patches involving the majority of his skin surface in a blaschkolinear pattern (**Figures 1 and 2**). The patient had no teeth at the time of examination. Examination of the eyes revealed matching eye color and no strabismus. Head control was indeed poor, and he had stiff joints of the hands and feet bilaterally. No laboratory work or biopsies were done. Based on the child's history and physical examination, a diagnosis of hypomelanosis of Ito was made. No specific treatments were rendered, but referrals were made to a geneticist, neurologist and orthopedic surgeon for evaluation and possible treatment. Since initial evaluation, the patient has been lost to follow-up.

Case 2

A 3-month-old male Indian infant presented to our clinic for concerns of pigmentation changes. The parents stated that at birth it was undetectable, but the pigmentation became pronounced by about six weeks of age. They had tried hydrocortisone lotion as well as emollients without improvement. Beyond his skin findings, the child has been eating well and meeting all milestones. Family history was reviewed and found to be non-contributory.

Physical examination showed the ventral aspect of the child's trunk, the proximal legs and the left forearm to have hypopigmented patches following a blaschkolinear pattern (**Figure 3**). The remaining body surfaces had no noticeable pigmentation changes. The child did not have teeth at the time of exam. There were no noticeable musculoskeletal abnormalities, and eye examination showed matching irises. The child's case was discussed with the pediatrician and the parents, and no referrals were made. Instead, we decided to continue to monitor the child's development and make further evaluations based on potential findings as they arise.

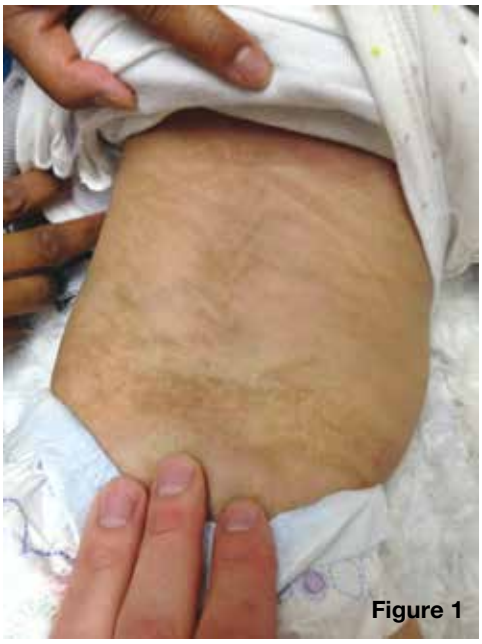

Figure 1

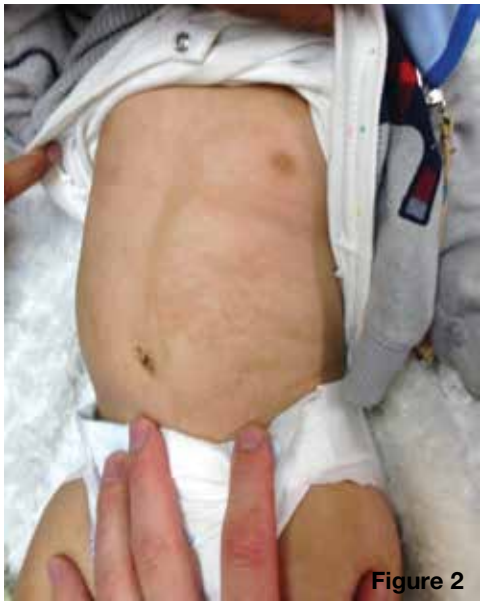

Figure 2

Figure 3

Discussion

Hypomelanosis of Ito (HI) is an uncommon syndrome presenting as hypopigmented whorls or streaks that generally follow the lines of Blaschko. This striking physical

Table 1. Diagnostic Criteria Proposed by Ruiz-Maldonado, et al[1]	
Criteria 1 (must have)	Congenital or acquired nonhereditary cutaneous hypopigmentation in linear streaks or patches involving more than two body segments
Major	1+ nervous system anomalies 1+ MSK anomalies
Minor	2+ congenital malformations other than neuro or MSK Chromosomal anomalies
Definitive dx	Criteria 1 and 1+ Majors, or Criteria 1 and 2+ Minors
Presumptive dx	Criteria 1 alone, or Criteria 1 with 1 minor

pattern represents chromosomal mosaicism in pigment production of the skin.[1] The majority of cases follow the blaschkolinear pattern, but occasionally checkerboard, dermatomal, phylloid and plaque-like patterns can be found.[2-4] The extent of involvement varies from segmental to total cutaneous involvement.[5] It presents within the first year of life in 75% of patients, with lighter-skinned children sometimes presenting as late as childhood. There is a slight female predominance.[6] Historically, HI had been described as incontinentia pigmenti achromians, as it appeared to be a negative image of incontinentia pigmenti, but this term has fallen out of favor because the two conditions are not related.

Associated systemic abnormalities are common, but hypopigmentation is the only constant feature and has wide phenotypic variability based on when gene defects occurred during embryologic migration.[5] As this condition is uncommon, and many mild cases likely go unreported, it is difficult to know the true number of HI cases that have associated systemic anomalies. Nehal et al. found that extracutaneous manifestations were only present in 33% of cases, and that the severity of these symptoms was directly correlated with the level of mosaicism, as with our two patients.[7]

Associated findings include neurologic, musculoskeletal (MSK), dental and ocular abnormalities.[5] Neurologic symptoms are most common, ranging from seizures to severe mental retardation. Musculoskeletal symptoms are also common and include abnormalities of the phalanges, limbs, spine, skull and sternum.[2,8-10] Dental abnormalities include anodontia and dysplasia. Strabismus and hypertelorism have been reported. Recently, an infant was diagnosed with HI and associated pulmonary hypoplasia.[11]

Diagnosis is clinical, based on the cutaneous findings, but associated symptoms may help identify HI. Some authors, however, only apply the term HI when there are extracutaneous symptoms associated with the hypopigmentation.[12] Alternative terms to use for patients with only cutaneous findings could be "linear nevoid

Table 2. Differential Diagnosis of Blaschkolinear Pigment Alteration		
Condition	**Presentation**	**Associated Findings**
Hypomelanosis of Ito	- Numerous genetic defects associated - Somatic mosaicism - Hypopigmented macules and papules that follow the lines of Blaschko - Covers more than two dermatomes - Often bilateral, but not symmetrical	- Central nervous system involvement (seizures, mental retardation) - Dental anomalies - Musculoskeletal abnormalities - Abnormal neural migration[1]
Incontinentia Pigmenti	- X-linked dominant, and deadly in males - NEMO gene mutation - Four stages: Newborns: linear papules and vesicles; eosinophilia Lesions progress to verrucous streaks that usually resolve 3-6 months: hyperpigmented whorls and swirls along Blaschko lines 2nd-3rd decade: hyperpigmented whorls become hypopigmented	- Scarring alopecia - Dystrophic nail changes - Anodontia or conical deformities of the teeth - Ophthalmologic problems - Central nervous system manifestations
Lichen Striatus	- Sudden eruption of erythematous or skin-toned linear papules - Usually asymptomatic, but can be pruritic - Active eruption lasts approximately 6-12 months - Post-inflammatory pigment alteration common for years - Unilateral	- Nail involvement possible. - No known associated systemic findings
Linear and Whorled Nevoid Hypermelanosis (LWNH)	- Also represents somatic mosaicism - Hyperpigmented and hypopigmented macules that follow lines of Blaschko - Present at birth or in infancy and continues to grow for 1-2 years, then stabilizes	- Variable, may have no findings - Central nervous system involvement - Musculoskeletal abnormalities - Heart abnormalities
McCune-Albright Syndrome	- GNAS1 mutation - Café-au-lait macules that follow the lines of Blaschko and present in infancy - Often unilateral - "Coast of Maine" border of café-au-lait macule	- Multiple endocrine abnormalities - Precocious puberty - Polyostotic fibrous dysplasia - Oral mucosal lentigines may present later in life
Focal Dermal Hypoplasia (Goltz Syndrome)	- X-linked dominant - Mutation in PORCN gene - Hypopigmented or hyperpigmented blaschkolinear lesions with associated dermal atrophy and telangiectasias	- Ectrodactyly (lobster-claw deformity) - "Raspberry-like" papillomas favoring perioral and perianal area - Ocular and dental abnormalities common

hypopigmentation" or "pigmentary mosaicism." This naming system seems ill-conceived, though, since the true effects of subtle neurologic and extracutaneous defects may not be evident until years later, as developmental milestones and speech progress, and the eventual recognition of those defects would require a renaming of the child's condition. We prefer to consider this a spectrum of disease and use HI to describe all patients with this phenotypic pattern.

In 1992, Ruiz-Maldonado et al. proposed criteria to diagnose HI, found in **Table 1**.[10] They based the criteria on clinical experience and previous reports, though they admit the criteria may not be accurate in diagnosing HI until its etiology has been found. They categorized the presence of chromosomal anomalies as a minor criterion, and present HI as a neurocutaneous syndrome. While significant advances have been made since this classification was introduced, it may still provide useful guidance for practitioners.

Mosaicism is the presence of two genetically distinct cell lines in a single person derived from a homogeneous zygote.[13-15] In embryogenesis, chromosomes are randomly distributed and migrate dorsoventrally along lines of Blaschko, resulting in two populations of epidermal skin with different pigment-producing potential. Phenotype varies greatly depending on the timing of the mutation and the cell lines affected. As would be expected, a mutation presenting earlier in embryologic development will have more widespread pigmentary mosaicism and be associated with more severe systemic findings.[7] Mutations occurring late in development are likely more segmental and associated with absent or mild systemic findings. Our two cases seem to support this.

Multiple genetic defects have been found in patients with HI. Thomas et al. found mosaicism in lymphocytes and skin fibroblasts along with autosomal or sex chromosomes.[4] Moss et al., however, found no dermal abnormalities but did find mosaicism within involved keratinocytes[16] Pascual-Castroviejo et al. recorded autosomal-dominant inheritance in some patients, but most cases appear to be sporadic.[9] Happle et al. published a case report of sporadic inheritance in a 26-year old male.[17] Despite the variation, four common genetic defects have been found: short arm of X-chromosome (XP11), short arm of chromosome 12, trisomy of chromosome 18, and triploides.[1,18] In addition, failure of X-inactivation (lyonization) may be responsible for sporadic cases of HI.[19]

Histopathologic examination could be useful if the diagnosis is in doubt, but it is not required in the evaluation of HI. Histology can show only subtle changes of fewer melanocytes and fewer, smaller melanosomes that do not produce sufficient pigment.[2,6] Cytogenetic analysis may reveal chromosomal mosaicism in the keratinocytes, but this test may not be available in all areas. Electron microscopy reveals fewer dendrites.[20-23] None of the histological, genetic or electron-microscopy findings are adequate to diagnose HI. Differentials for hypopigmentation that follow Blaschko lines can be found in **Table 2**.

Presentations of HI may vary, and it is important to perform a thorough examination to identify any concurrent musculoskeletal, neurologic, dental and ocular symptoms. Identification of hypopigmentation can be made with histology, genetic testing and Wood's light. Once HI is suspected, optional testing includes radiography for skeletal abnormalities, electromyelography (EMG) for muscle function, head CT or MRI, ophthalmologic exam, and electroencephalography (EEG) if seizures are present. Magnetic resonance imaging appears to be the most sensitive test to visualize neural migration abnormalities.[24,25] It is prudent to involve primary care, orthopedic or physical medicine specialists, and neurologists (as needed) early in the patient's life. A referral to a geneticist is also likely warranted.

Conclusion

There are no specific treatments for hypomelanosis of Ito, but prompt identification of associated findings may improve prognosis in patients. Once identified, early involvement of a multidisciplinary team is warranted based on the extracutaneous findings. The striking physical findings are a result of pigmentary and chromosomal mosaicism, but there is still much to be learned about the genetic mutations leading to these findings. With improved knowledge, more focused workups and treatments may be available in the future.

References

1. Hamosh A. Hypomelanosis of Ito. HMI Johns Hopkins University. 2001 [updated 2011; cited 2014]. Available from: http://www.omim.org/entry/300337?search=hypomelanosis of ito&highlight=hypomelanosi of ito.

2. Kuster W, Konig A. Hypomelanosis of Ito: no entity, but a cutaneous sign of mosaicism. Am J Med Genet. 1999;85(4):346-50.

3. Metzker A, Morag C, Weitz R. Segmental pigmentation disorder. Acta Derm Venereol. 1983;63(2):167-9.

4. Thomas IT, Frias JL, Cantu ES, Lafer CZ, Flannery DB, Graham JG, Jr. Association of pigmentary anomalies with chromosomal and genetic mosaicism and chimerism. Am J Hum Genet. 1989;45(2):193-205.

5. Ponti G, Pellacani G, Tomasi A, Percesepe A, Guarneri C, Guerra A, et al. Hypomelanosis of Ito with a trisomy 2 mosaicism: a case report. J Med Case Rep. 2014;8:333.

6. Sharma S, Gupt R, Saxena GN, Raghu MS, Patodi A. Hypomelanosis of Ito. J Assoc Phys India. 2014;62(1):47-8.

7. Nehal KS, PeBenito R, Orlow SJ. Analysis of 54 cases of hypopigmentation and hyperpigmentation along the lines of Blaschko. Arch Dermatol. 1996;132(10):1167-70.

8. Jelinek JE, Bart RS, Schiff SM. Hypomelanosis of Ito ("incontinentia pigmenti achromians"). Report of three cases and review of the literature. Arch Dermatol. 1973;107(4):596-601.

9. Pascual-Castroviejo I, Lopez-Rodriguez L, de la Cruz Medina M, Salamanca-Maesso C, Roche Herrero C. Hypomelanosis of Ito. Neurological complications in 34 cases. Can J Neurol Sci. 1988;15(2):124-9.

10. Ruiz-Maldonado R, Toussaint S, Tamayo L, Laterza A, del Castillo V. Hypomelanosis of Ito: diagnostic criteria and report of 41 cases. Pediatr Dermatol. 1992;9(1):1-10.

11. Bhat RY, Patra S, Varma PV, Prakashini K. Hypomelanosis of Ito with an unusual pulmonary abnormality in an infant. Indian Dermatol Online J. 2014;5(2):196-7.

12. Hall BD. Of mice, persons, and pigment. Am J Hum Genet. 1989;45(2):191-2.

13. Donnai D, Read AP, McKeown C, Andrews T. Hypomelanosis of Ito: a manifestation of mosaicism or chimerism. Am J Med Genet. 1988;25(12):809-18.

14. Ritter CL, Steele MW, Wenger SL, Cohen BA. Chromosome mosaicism in hypomelanosis of Ito. Am J Med Genet. 1990;35(1):14-7.

15. Sybert VP, Pagon RA, Donlan M, Bradley CM. Pigmentary abnormalities and mosaicism for chromosomal aberration: association with clinical features similar to hypomelanosis of Ito. J Pediatr. 1990;116(4):581-6.

16. Moss C, Larkins S, Stacey M, Blight A, Farndon PA, Davison EV. Epidermal mosaicism and Blaschko's lines. J Med Genet. 1993;30(9):752-5.

17. Happle R. Incontinentia pigmenti versus hypomelanosis of Ito: the whys and wherefores of a confusing issue. Am J Med Genet. 1998;79(1):64-5.

18. Koiffmann CP, de Souza DH, Diament A, Ventura HB, Alves RS, Kihara S, et al. Incontinentia pigmenti achromians (hypomelanosis of ITO, MIM 146150): further evidence of localization at Xp11. Am J Med Genet. 1993;46(5):529-33.

19. Hatchwell E, Robinson D, Crolla JA, Cockwell AE. X inactivation analysis in a female with hypomelanosis of Ito associated with a balanced X;17 translocation: evidence for functional disomy of Xp. J Med Genet. 1996;33(3):216-20.

20. Grosshans EM, Stoebner P, Bergoend H, Stoll C. [Incontinentia pigmenti achromians (ITO). Clinical and histopathological study]. Dermatologica. 1971;142(2):65-78.

21. Happle R, Krenz J, Pfeiffer R. [Ito's syndrome (incontinentia pigmenti achromians)]. Hautarzt. 1976;27(6):286-90.

22. Nordlund JJ, Klaus SN, Gino J. Hypomelanosis of Ito. Acta Derm Venereol. 1977;57(3):261-4.

23. Saxena U, Ramesh V, Iyengar B, Misra RS. Hypomelanosis of ito: histochemical and ultrastructural observations. Australas J Dermatol. 1989;30(1):45-7.

24. Ardinger HH, Bell WE. Hypomelanosis of Ito. Wood's light and magnetic resonance imaging as diagnostic measures. Arch Neurol. 1986;43(8):848-50.

25. Lungarotti MS, Martello C, Calabro A, Baldari F, Mariotti G. Hypomelanosis of Ito associated with chromosomal translocation involving Xp11. Am Journal Med Genet. 1991;40(4):447-8.

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