

Blue Colon at Autopsy

To the Editor.—Recently we encountered a blue colon at autopsy (Figure). The recently published article by Boutilier et al¹ and their photograph illustrating a green colon were instrumental in determining the probable origin of the unusual finding of this bright blue colon. The autopsy was performed on a 50-year-old diabetic woman who was status postnephrectomy for xantho-granulomatous pyelonephritis. She had been in the surgical intensive care unit for 34 days prior to her death. During this time she received enteral feeding by the aspiration detection protocol calling for 0.5 mL of blue food color per 250 mL of food given. The active ingredient in this product is FD&C Blue No. 1 (Warner-Jenkinson, St Louis, Mich), also commonly known as “brilliant blue.” This patient had a similarly colored bright blue colon and some less intensely stained patchy blue areas in the small intestine. No other organs were blue. Similar to the cases with green colons, the entire length of the colon was blue and the mucosa was as brightly stained as the serosa. No other abnormality was found in the colon, and the patient had no history of significant gastrointestinal symptoms. Histologic examination of the colon did not show blue discoloration or abnormalities, with the exception of moderate autolysis.

FD&C Blue No. 1 was hypothesized to have caused refractory hypotension and metabolic acidosis in 2 patients who died.² The Food and Drug Administration approved the blue food coloring based on experiments performed on healthy animals, which demonstrated the dye to be nonabsorbable. Now there are case reports of humans in which the dye may have been absorbed.^{2,3} Absorbed dye is likely excreted by the kidneys.⁴ Our patient had 1 remaining kidney, which was found on histologic examination to have nodular and diffuse glomerulosclerosis con-



Blue discoloration in a colon found at autopsy of a 50-year-old woman who had received enteral feedings tinted with FD&C Blue No. 1.

sistent with diabetic nephropathy. However, she did not have any clinical evidence of renal insufficiency. Due to the lack of information on the effects of FD&C Blue No. 1 given to patients with renal disease, it is not possible to determine if the blue color of the bowel was related to nephropathy or was merely an incidental finding. Clearly there is a need for more research on the safety of FD&C Blue No. 1 in critically ill patients. Pathologists can make an important contribution by thoroughly documenting any unusual discoloration found at autopsy.

The photograph was taken by Scott Sharples, fourth-year medical student at Baylor College of Medicine, Baylor, Tex.

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1. Boutilier RG, Murray SK, Walley VM. Green colon, an unusual appearance at autopsy. *Arch Pathol Lab Med.* 2000;124:1397–1398.
2. Maloney JP, Halbower AC, Fouty BF, et al. Systemic absorption of food dye in patients with sepsis. *N Engl J Med.* 2000;343:1047–1048.
3. Metheny M, Clouse RE. Bedside methods for detecting aspiration in tube-fed patients. *Chest.* 1997;111:724–731.
4. Bjarnason I, MacPherson A, Hollander D. Intestinal permeability: an overview. *Gastroenterology.* 1995;108:1566–1581.

Tumors and Hypomelanosis of Ito

To the Editor.—We read with interest the article by Xu et al¹ reporting on the occurrence of a primary meningeal rhabdomyosarcoma in a 15-month-old boy with hypomelanosis of Ito (HI). The report is intriguing because of the rarity of the tumor per se and its association to HI. However, in light of the most recent clinical

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Review of Cases of Hypomelanosis of Ito Associated With Tumors*

Reference	Sex/Age	Skin Features (Hypopigmentation)	Other Associated Features	Tumor Type	Cytogenetic Analysis
Browne and Byrne, ¹¹ 1976	F/3 y	Streaks, diffuse, face + trunk + extremities	Cicatricial alopecia; wholly hair	Teeth, deciduous complex composite odontome	ND
Tateno et al, ¹⁷ 1981	F/NR	Linear + streaks	NR	Blood, acute lymphatic leukemia	ND
Happle and Vakilzadeh, ¹² 1982	F/4 y	Linear + patchy, diffuse, LB, trunk + extremities	Pigmentation iris + retina	Teeth, primary + permanent talon cusp odontome (hamartomatous)	ND
Ishikawa et al, ¹³ 1985	M/14 y	Streaks + patches, L, diffuse, histology = normal	Developmental delay, VSD, sensory neuropathy, left temporal bony defect, dysmorphic signs, seizures conical teeth	Skull, diploic dermoid cyst Mediastinum, mature cystic teratoma connective tissue, cartilage, smooth muscle, mucous glands)	45,XY,-14,-21,+t(14q21q) 46,XY,-14,-21,+t(14q21q)+m mosaic, lymphocytes
Turleau et al, ¹⁴ 1986	F/1 y	Linear patches, trunk + extremities	Developmental delay, seizures, hand dysmorphism, body hemiatrophy (L), chorioretinal atrophy, agenesis corpus callosum, hypoplasia vermis	Sacrocoecygeum, complex dysembrioma of mature tissue	Microdeletion 15q1 (q11 or q13), 50% lymphocytes
Steichen-Gersdorf et al, ¹⁵ 1993 Zajac et al, ¹⁶ 1997	F/5 y	Streaks + whorls, LB, trunk + extremities	Macrocephaly, dysmorphic, nevoid pigmentation eye; developmental delay	Brain, isomorphic plexus papilloma, grade 1	46,XX, X;17 (q12;p13), lymphocytes, tumor
Steiner et al, ¹⁸ 1996	M/9 y	Linear + streaks, >2 limbs or 1 limb + trunk	Deafness	Brain, medulloblastoma IV ventricle	46,XY (normal), lymphocytes, tumor
Oguma et al, ¹⁹ 1996	F/6 mo	Linear + whorled, LB, trunk + extremities	Sindactyly	Adrenal gland, poorly differentiated, ganglioneuroblastoma, grade 1	ND
Xu et al, ¹ 2000	M/15 mo	Linear + whorled, trunk + abdomen	Hydrocephalus, seizures	Brain, meninges, embryonal rhabdomyosarcoma	ND

* NR indicates not recorded; LB, along the lines of Blaschko; L = left; VSD, ventricular septal defect; and ND, not done.

and genetic studies on HI, we would like to add some comments on (1) the incidence of associated systemic features and current diagnostic criteria, (2) recent cytogenetic findings, and (3) its association with tumors.

The term *hypomelanosis of Ito* is applied to individuals with skin hypopigmentation along the lines of Blaschko.^{2,3} However, because of conflicting reports about the frequency of associated extracutaneous abnormalities (mostly of the central nervous, musculoskeletal, and ocular systems) and disagreement over terminology, HI still represents a controversial issue in the medical literature.^{2,3}

One explanation for the discrepancy in figures for associated abnormalities could be that earlier studies were based on limited and biased cases. These reports tended to describe the most severely affected patients with multiple abnormal systemic features who were referred to tertiary care centers for diagnosis and management. Lower incidences

(33% to 66%) of associated extracutaneous findings were demonstrated by dermatology and pediatric dermatology groups,⁴ while higher frequencies (80% to 94%) have been reported by neurology and pediatric neurology groups.⁵

Things are further complicated by current diagnostic criteria,⁶ which are not sufficiently restricted, as highlighted by recent studies.²⁻⁴ In fact, according to the sine qua non criterion ("presence of skin hypopigmentation in linear streaks or patches involving more than two body segments"⁶) a significant number of individuals can be diagnosed as having HI because of the presence of diffuse or patchy, generalized or limited, linear or spotty skin depigmentation or hypopigmentation distributed along the lines of Blaschko, but also in many other configurations. In addition, 2 other criteria,⁶ precisely, involvement of the nervous or musculoskeletal systems (major criterion) or presence of other (unspecified) congenital malformations or chromo-

somal anomalies (minor criterion), are considered as additional features for making a diagnosis of HI. However, the association of nervous system or musculoskeletal abnormalities with linear or patchy pigmentary skin anomalies is encountered in many clinical conditions other than HI.⁷ These are probably some of the causes that contributed to generating confusion and to expanding the phenotype of HI by lumping together patients previously thought to have different conditions and combining under the same rubric several disorders of different etiologies. Notably, in the *London Dysmorphology Database*⁷ (a computerized catalog of dysmorphic-neurogenetic disorders), 65 different syndromes (including HI) are listed under the same entry "patchy depigmentation of skin."

A number of reports have claimed familial occurrence, supporting single-gene inheritance for HI, but none has been proved.^{2,3,8} Miscellaneous chromosomal abnormalities have been demonstrated in some but not

all affected individuals and are currently classified into 2 groups^{3,9}: (1) various mosaicism for almost any autosome or sex chromosomes and (2) nonmosaic balanced X;autosome translocations with breakpoints in the juxtacentromeric region of the X chromosome at Xp11 found so far in a limited group of girls with HI.⁹ Such mosaicism is generally not transmissible from one generation to the next, and this could explain the sporadic occurrence of the disorder. There could be some reasons for lack of demonstration of chromosomal mosaicism in all individuals with HI¹⁰: (1) most cytogenetic studies have been directed so far at peripheral lymphocytes or at cultured fibroblasts obtained from skin biopsies rather than at cultured keratinocytes or melanocytes (lines of Blaschko are epidermal not dermal), and (2) some genetic mosaicisms are too subtle to be detected by current techniques. Thus, despite current lack of a definitive genetic explanation, it has been suggested that HI is not a single condition, but a rather nonspecific manifestation (ie, a phenotype) of different chromosomal mosaicism and that the term *hypomelanosis of Ito* should now be dropped.^{2,3,9,10} Proposed changes to terminology, so far, include the terms *pigmentary dysplasia*, *mosaic dyspigmentation*, *pigmentary mosaicism of the Ito type*, or *hypopigmentation along the lines of Blaschko* to reflect the disease pathogenesis or recall the cutaneous patterns.^{9,10}

A limited number of HI cases are associated with benign^{11–16} and malignant^{1,17–19} tumors (Table). When peripheral blood lymphocytes and tumor specimens have been searched

for chromosomal abnormalities (as in 4 of the 9 reported cases), they were found (Table). We did not observe tumors in any of the 41 patients with HI (aged 2 to 40 years) seen at our institution, of whom 45% harbored chromosomal anomalies (unpublished data).²⁰ Similar findings were recorded in the largest series reported to date.^{4–6,18} Notably, almost all reported tumors in HI (Table) share a common embryonal origin,^{1,11–13,15–17,19} in accordance to what was postulated by Xu et al.¹ In addition, these tumors present during the first years of life, confirming that parents should be reassured that serious complications in HI, if present, are typically evident early in infancy.⁴

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1. Xu F, De Las Casas LE, Dobbs LJ. Primary meningeal rhabdomyosarcoma in a child with hypomelanosis of Ito. *Arch Pathol Lab Med.* 2000;124:762–765.

2. Sybert V. Hypomelanosis of Ito: a description, not a diagnosis. *J Invest Dermatol.* 1994;103:141S–143S.

3. Kuster W, Konig A. Hypomelanosis of Ito: no

entity, but a cutaneous sign of mosaicism. *Am J Med Genet.* 1999;85:346–350.

4. Nehal KS, PeBenito R, Orlow SJ. Analysis of 54 cases of hypopigmentation and hyperpigmentation along the lines of Blaschko. *Arch Dermatol.* 1996;132:1167–1170.

5. Pascual-Castroviejo I, Roche C, Martinez-Bermejo A, et al. Hypomelanosis of Ito: a study of 76 infantile cases. *Brain Dev.* 1998;20:36–43.

6. Ruiz-Maldonado R, Toussaint S, Tamayo L, Larterza A, Castillo VD. Hypomelanosis of Ito: diagnostic criteria and report of 41 cases. *Pediatr Dermatol.* 1992;9:1–10.

7. Winter RM, Baraitser M. *The London Dysmorphology Database.* Oxford, England: Oxford University Press; 2000.

8. Ruggieri M. Familial hypomelanosis of Ito: implications for genetic counselling. *Am J Med Genet.* 2000;95:82–84.

9. Hatchwell E. Hypomelanosis of Ito and X;autosome translocations: a unifying hypothesis. *J Med Genet.* 1996;33:177–183.

10. Moss C, Savin J. *Dermatology and the New Genetics.* Oxford, England: Blackwell Science; 1995: 3–35.

11. Browne RM, Byrne JPH. Dental dysplasia in incontinentia pigmenti achromians (Ito): an unusual form. *Br Dent J.* 1976;140:211–214.

12. Happel R, Vakilzadeh F. Hamartomatous dental cusps in hypomelanosis of Ito. *Clin Genet.* 1982;21:65–68.

13. Ishikawa T, Kanayama M, Sugiyama K, et al. Hypomelanosis of Ito associated with benign tumours and chromosomal abnormalities: a neurocutaneous syndrome. *Brain Dev.* 1985;7:45–49.

14. Turleau C, Taillard F, Doussau de Bazignan M, et al. Hypomelanosis of Ito (incontinentia pigmenti achromians) and mosaicism for a microdeletion of 15q1. *Hum Genet.* 1986;74:165–187.

15. Steichen-Gersdorf E, Trawogger R, Duba HC, et al. Hypomelanosis of Ito in a girl with plexus papilloma and translocation (X;17). *Hum Genet.* 1993; 90:611–613.

16. Zajac V, Kirchhoff T, Levy ER, et al. Characterisation of X;17(q12q13) translocation breakpoints in a female patient with hypomelanosis of Ito and choroid plexus papilloma. *Eur J Hum Genet.* 1997; 5:61–68.

17. Tateno A, Sasaki S, Tsukimoto I, Mizuno K. A case of incontinentia pigmenti achromians with acute lymphatic leukemia. *Shonika Rinsho.* 1981; 34:831–835.

18. Steiner J, Adamsbaum C, Desguerres I, et al. Hypomelanosis of Ito and brain abnormalities: MRI findings and literature review. *Pediatr Radiol.* 1996; 26:763–768.

19. Oguma E, Aihara T, Shimanuki Y, et al. Hypomelanosis of Ito associated with neuroblastoma. *Pediatr Radiol.* 1996;26:273–275.

20. Ruggieri M, Pavone L. Hypomelanosis of Ito: clinical syndrome or just phenotype? *J Child Neurol.* 2000;15:635–644.