Figure 3.2 **Female androgenetic alopecia. Concomitant presence of thick, intermediate, and thin hair shafts is called hair shaft thickness heterogeneity. This is a trichoscopy manifestation of nonsimultaneous hair miniaturization.**

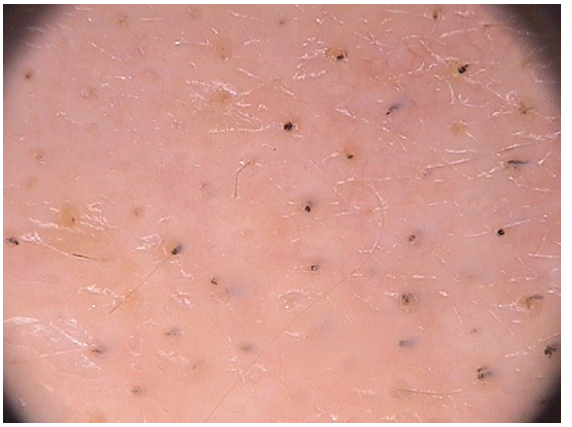

Figure 3.3 **Alopecia areata. Concomitant presence of regularly distributed yellow dots and black dots. The black dots reflect an active phase of disease.**

Hair shaft thickness heterogeneity, with simultaneous presence of thin, intermediate, and thick hairs, is the most characteristic feature of androgenetic alopecia. It has been shown that hair diameter diversity reflects follicle miniaturization in androgenetic alopecia.[14,15] Precise evaluation of hair shaft thickness in micrometers is not essential for clinical diagnosis but may be useful for monitoring treatment efficacy[16] and is indispensable for clinical trials.[10] Another trichoscopy feature of androgenetic alopecia is increased proportion of vellus hairs. The number of hairs in one follicular unit is decreased in androgenetic alopecia. Follicular units with only one hair predominate in these patients, especially in the frontal area.[17–19] The presence of yellow dots is a constant finding in androgenetic alopecia. These yellow dots mark mainly empty hair follicles with sebum.[17] These sebaceous yellow dots may be washed away by a vigorous hair wash. Thus, patients should not wash their hair directly preceding a trichoscopy examination. Brown perifollicular discoloration (peripilar sign)[20] is observed in 20%–66% of patients with androgenetic alopecia.[15,17] A proportion of about 30% of hair follicle openings is usually affected.[15,17]

Trichoscopy of senescent (senile, involutionary) alopecia shares with androgenetic alopecia a predominance of follicular units with only one hair, decreased hair shaft density with a honeycomb pattern pigmentation, and slight tendency to form brown perifollicular discoloration (peripilar sign).[12]

ALOPECIA AREATA

The most common trichoscopy features of alopecia areata (Figure 3.3) are regularly distributed yellow dots, exclamation mark hairs, tapered hairs, and black dots. Trichoscopy of alopecia areata may differ depending on disease activity, severity, and duration.[21] Lacarrubba et al.[6] identifi d three features of acute alopecia areata: micro-exclamation marks, black dots, and vellus hairs. Inui et al.[22] identifi d similar markers of disease activity (black dots, tapering hairs, and broken hairs) in another study. The experience of my team[3,23] shows that black dots and exclamation mark hairs are a constant marker of disease activity in alopecia areata.

Pohl-Pinkus constrictions and monilethrix-like hairs are observed in less than 5% of patients with alopecia areata.[24,25]

TRICHOTILLOMANIA

Trichotillomania (Figure 3.4) is a common and difficult differential diagnosis of alopecia areata.[26] Trichoscopy of

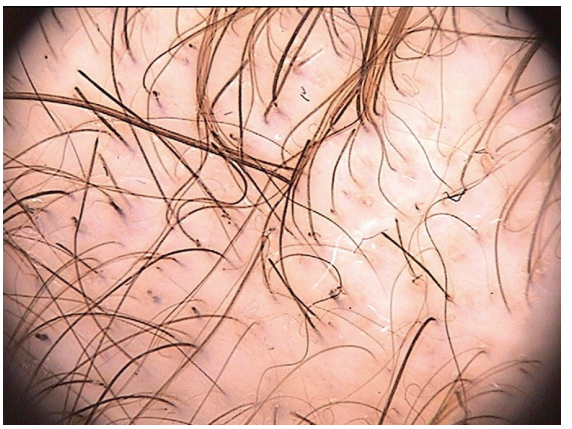

Figure 3.4 **Trichotillomania. The simultaneous presence of multiple hairs broken at different lengths (in the absence of exclamation mark hairs) may be indicative of trichotillomania.**

trichotillomania shows hairs broken at different lengths. Irregular coiled hairs[5] and flame hairs[23] are the most characteristic trichoscopy findings in trichotillomania. Other findings include short hairs with trichoptilosis ("split ends"), upright regrowing hairs, black dots, and the v-sign.[12,23,26–28] High-power trichoscopy (performed with a digital videodermoscope) may reveal the presence of hair residue particles, called "hair powder."[23] Exclamation mark hairs are rare in trichotillomania, but they may be a diagnostic pitfall and cause misdiagnosis of alopecia areata.[2,23]

TINEA CAPITIS

Slowinska et al. described comma hairs[29] as a characteristic feature of tinea capitis (Figure 3.5). Later, Hughes et al. identified corkscrew hairs[30] as another characteristic finding in patches of tinea capitis. Recent findings show also zigzag hairs and interrupted (Morse code–like) hairs are observed in these patients.[2,3] Ultraviolet (UV)-enhanced trichoscopy (UVET) (Figure 3.6), which is a combination of trichoscopy and Wood's light, may further aid in screening patients for tinea capitis.[3]

DISCOID LUPUS ERYTHEMATOSUS

The most characteristic trichoscopy features of discoid lupus erythematosus (Figure 3.7) localized on the scalp are thick arborizing vessels and large yellow dots.[2,25,31] Scattered brown discoloration of the skin may be observed in some patients.[2,25,31] Yellow dots with radial, thin arborizing vessels emerging from the dot are considered characteristic for discoid lupus erythematosus. This feature is sometimes referred to as "red spider in yellow dot."[32] Red dots, described by Tosti et al.,[10] are considered a good prognostic factor for hair regrowth. Long-lasting, inactive lesions with prominent fibrosis show structureless milky-red areas and lack of follicular openings in trichoscopy.[7]

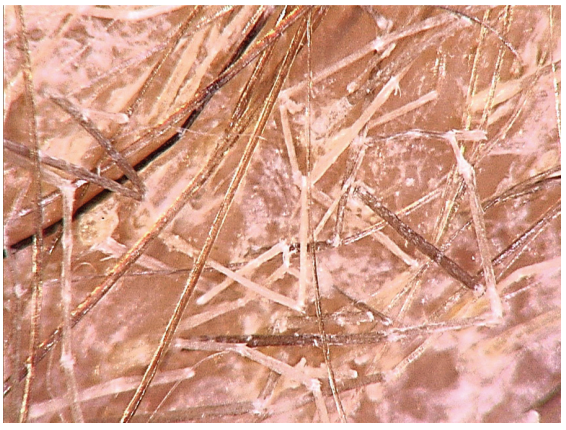

Figure 3.5 **Tinea capitis. The image shows multiple zigzag hairs in a patient with *Microsporum canis*–induced alopecia.**

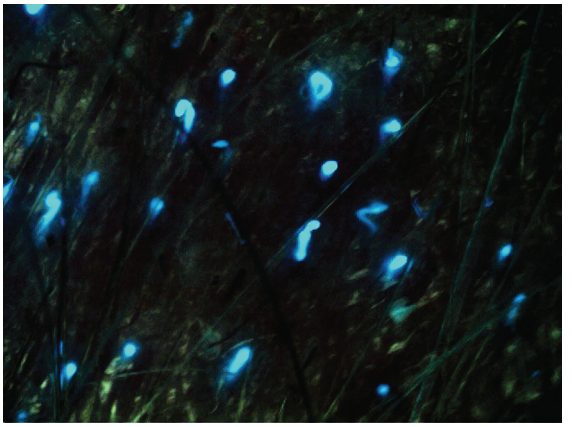

Figure 3.6 **UVET (UV-enhanced trichoscopy) is a combination of trichoscopy with Wood's light. The image shows fluorescence of multiple comma hairs infected with *Microsporum canis*.**

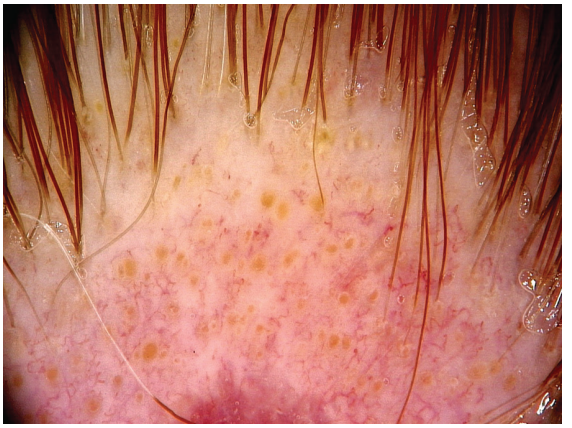

Figure 3.7 **Discoid lupus erythematosus. Trichoscopy shows arborizing vessels, large (keratotic) yellow dots at the hair-bearing margin of a scalp lesion.**

LICHEN PLANOPILARIS AND FRONTAL FIBROSING ALOPECIA

The most characteristic trichoscopy feature of classic lichen planopilaris (Figure 3.8) is white perifollicular scaling with scales entangling hair shafts up to 2–3 mm above scalp surface. My team called this phenomenon "tubular scaling."[7] Other findings include perifollicular inflammation, elongated blood vessels, and violaceous-blue interfollicular areas.[7,33,34] In the late fibrotic stage of lichen planopilaris, the predominating features are fibrotic white dots, which merge into white and/or milky-red areas.[2,7]

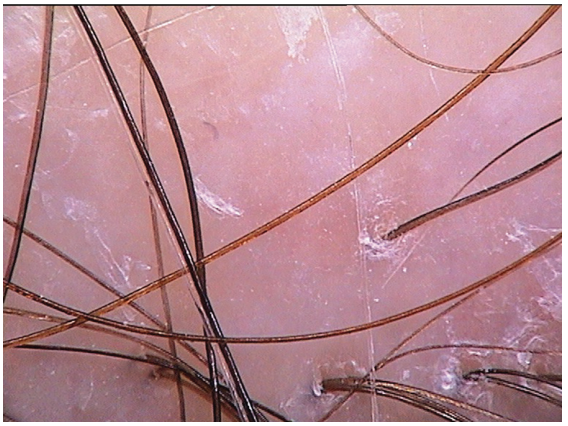

Figure 3.8 **Lichen planopilaris. Perifollicular scaling and a milky-red (strawberry ice cream color) area lacking follicular openings.**

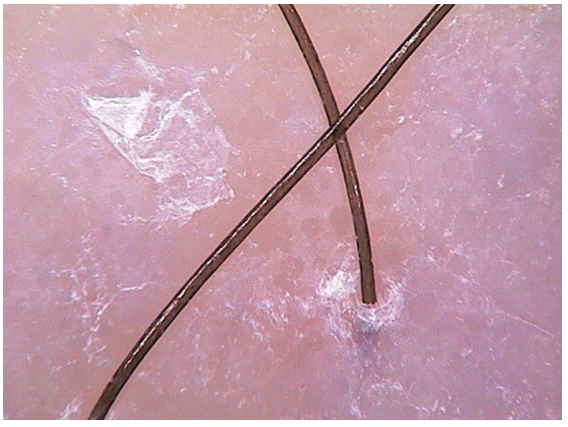

Figure 3.9 **Frontal fibrosing alopecia. A lonely hair surrounded by a fibrotic area.**

Trichoscopy findings in active frontal fibrosing alopecia (Figure 3.9) are similar but significantly less prominent. These features include minor perifollicular scaling and predominance of follicular openings with only one hair. The dark, terminal, "lonely hairs" surrounded by ivory-colored fibrotic areas may be seen both clinically as well as trichoscopically.[35]

DISSECTING CELLULITIS

In dissecting cellulitis (Figure 3.10) (dissecting folliculitis, perifolliculitis capitis abscedens et suffodiens), trichoscopy shows yellow, structureless areas. Characteristic trichoscopy fi dings include yellow "3D" dots imposed over dark hair shaft residues, pinpoint-like vessels with whitish halo, and confluent ivory-white areas lacking follicular openings in end-stage disease with prominent fibrosis.

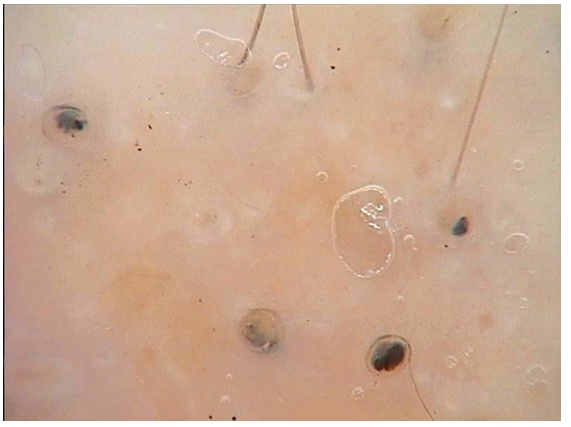

Figure 3.10 **Dissecting cellulitis. 3D yellow dots superimposed over black hair residues.**

FOLLICULITIS DECALVANS

Folliculitis decalvans (Figure 3.11) is characterized by the presence of multiple hairs in one follicular unit.[36] These follicular tufts usually consist of 5–20 hairs.[36] This feature may be observed both clinically and by trichoscopy. Additional trichoscopy findings include follicular pustules, perifollicular tubular scaling, and hyperplasia arranged in a starburst pattern.[37] The scales that entangle hair shafts in a tubular manner are characterized by a yellowish color and a tendency to fold away from the hair shafts in a collar-like fashion.[2] In end-stage fibrotic lesions, white or milky-red (strawberry ice cream color) areas lacking follicular openings predominate.[7]

GENETIC HAIR SHAFT ABNORMALITIES

Trichoscopy is a perfect tool for noninvasive evaluation of most genetic hair shaft abnormalities.[1,38,39] It has been

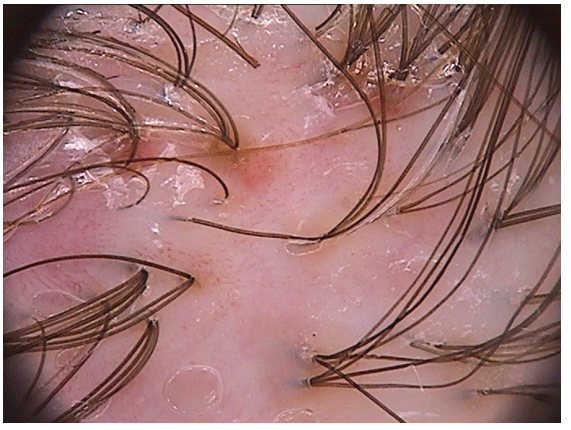

Figure 3.11 **Folliculitis decalvans. Hair tufts emerging from inflammatory areas. The milky-red area in the mid-part of the image indicates fibrosis of recent onset.**

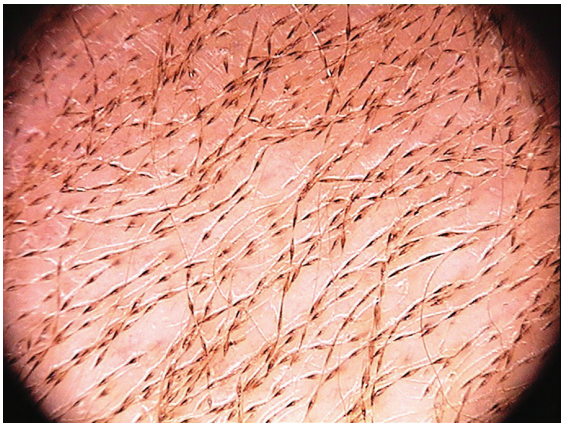

Figure 3.12 **Monilethrix. Trichoscopy easily replaces light microscopy in examination of hair shafts for genetic structure abnormalities.**

documented that trichoscopy allows for the detection of characteristic structural abnormalities of monilethrix,[40–44] (Figure 3.12) trichorrhexis invaginata,[43,45,46] trichorrhexis nodosa,[43] pili torti,[43] and pili annulati[43] without the need to pull hairs for light microscopy examination.[47]

APPLICATION OF TRICHOSCOPY IN CLINICAL TRIALS, RESEARCH, AND MONITORING TREATMENT EFFICACY

Trichoscopy is a precise, excellent tool for monitoring treatment efficacy in everyday practice and in clinical trials. Th s method allows quantitative evaluation of hair shaft thickness, number of hairs per follicular unit, number of empty hair follicles, and multiple other parameters. For the purpose of research and clinical trials, the examination should be performed in a standardized manner.[2,18]

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4 Hair dysplasias

Juan Ferrando, L. Alheli Niebla, and Gerardo A. Moreno-Arias

INTRODUCTION

Hair dysplasia means an alteration of the hair shaft. Most cases are congenital, some are hereditary, and others are acquired (e.g., bubble hair). It may involve a localized or generalized defect, but always follows a characteristic morphological pattern.[1,2] The defect may be restricted to the hair or constitute a diagnostic clue for a genodermatosis (e.g., Netherton syndrome and trichothiodystrophy). Classification of hair dysplasias is difficult, but in practical terms we accept the classification as presented in Table 4.1.[3–6] The main clinical and morphological diagnostic characteristics of hair dysplasias are discussed in this chapter.

MONILETHRIX

This is an AD (autosomal dominant) defect of the hair shaft. Hair is short, just a few millimeters long, and beaded. Breaking of the hair shaft occurs as soon as hair goes out of the *ostium*, due to narrowing segments of the shaft. Focal follicular hyperkeratosis and marked hypotrichosis may also be seen. It generally affects some individuals of different generations of the same family. The morphological defect is the periodical narrowing of the hair shaft, which may be seen deep in the hair follicle in biopsy specimens.[4,7,8]

Table 4.1 Classification of Hair Dysplasia

Hair dysplasia with hair fragility:
Monilethrix
Pseudomonilethrix
Pili torti
Menkes syndrome (kinky hair)
Trichorrhexis invaginata (Netherton syndrome)
Trichothiodystrophy
Trichonodosis
Distal trichorrhexis nodosa
Proximal trichorrhexis nodosa
Bubble hair
Loose anagen hair
Hair dysplasia with no or little hair fragility:
Pili annulati
Pseudopili annulati
Diffiuse woolly hair
Woolly hair nevus
Acquired progressive kinking of hair
Diffuse partial *woolly hair*
Acquired partial curly hair
Straight hair nevus
Pili canaliculi

Genetics. Monilethrix is an autosomal dominant hereditary defect caused by mutation of genes *hHb1*, *hHb3*, and *hHb6* localized in chromosome (cr) band 12q13 that encodes diverse trichokeratins. We reported a new family with a change in the nucleotide in heterozygosis of position 154 of exon1 of gen *KRT81* (154G > C). In the DNA sequence, this substitution involves a change of one amino acid in a protein (glycine for arginine in position 52). Interruption of keratin synthesis may be the cause of periodic variation of hair shaft diameter. Autosomal recessive (AR) cases have also been reported and are due to a gene mutation (18q) that encodes desmoglein 4 (*DSG4*), a situation that affects affinity for plakoglobin and alters hair shaft esmosomes.[9–12]

Clinical diagnosis. The clinical picture includes diffuse hypotrichosis and short, fragile, and beaded hairs. Localized (occipital region) or generalized marked follicular hyperkeratosis may also be seen (Figure 4.1).

Optical microscopy. Alternating periodical beading (defect) and knots (normal hair shaft diameter), is characteristic, may also be seen in dermoscopy (Figure 4.2).

Scanning electron microscopy. Microscopic images are similar to those observed in optical microscopy: hair shaft racture is evidenced in narrowed segments.

Trichoscopy. Dermoscopy is a useful tool in order to see follicular hyperkeratosis in the proximal segment of the hair. The typical image of "pearl necklace" refers to elliptical beading, regularly separated by narrowing segments where hair shaft fracture is usually observed. The hair shaft diameter is normal in the beaded segment of the hair shaft, and medulla is observed, while this is not seen in the narrowed segments. These findings are easily identified by dermoscopy, a simple method for a quick diagnosis (Figure 4.3).[13–14]

Histology. Intrafollicular hair shaft narrowing is observed.

PSEUDOMONILETHRIX

Pseudomonilethrix is a rare AD defect characterized by hair fragility. Localized or diffuse hypotrichosis and fake knots (irregular hair shaft flattening) occur as the result of compulsive and frequent combing of the hair. Follicular

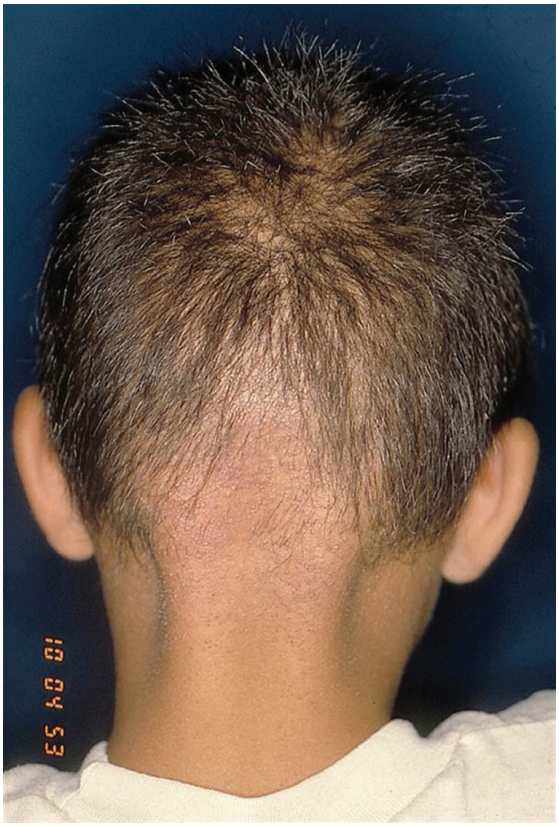

Figure 4.1 **Diffuse hypotrichosis with severe hyperkeratosis follicularis in the occipital region is characteristic.**

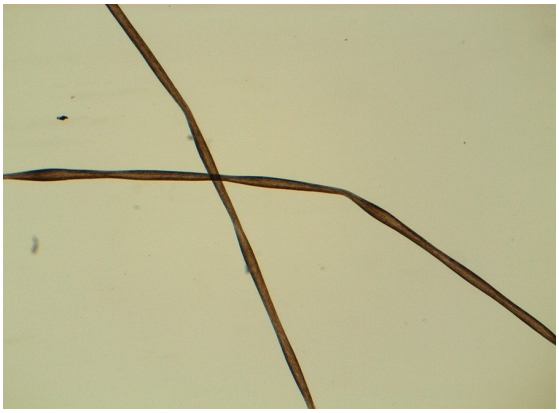

Figure 4.2 **Typical beading with alternating knots and narrowed segments.**

hyperkeratosis is not observed. Individuals of different generations may be affected in the same family.[15,16] It may be associated with *trichorrhexis nodosa* and *bubble hair.*

Genetics. It is an AD defect. Specific genetic alterations have not yet been reported.

Figure 4.3 **Elliptical beading with narrowed segments are seen on trichoscopy.**

Clinical diagnosis. It is a familiar localized or diffuse hypotrichosis without follicular hyperkeratosis.

Optical microscopy. There are rounded, normal appearing hairs with scarce and irregular oval/round knots. Hair shaft arrowing is not observed (Figure 4.4).

Electron microscopy. "Knots" actually are flat segments of the hair shaft Figure 4.5).

Trichoscopy. There are irregular oval/round nodules without hair shaft narrowing segments and alternating normal/wider segments of the hair shaft. No follicular hyperkeratosis is observed.

ACQUIRED OR IATROGENIC PSEUDOMONILETHRIX (PSEUDOPSEUDOMONILETHRIX)

This is a similar defect as *pseudomonilethrix* due to improper hair handling. It occurs when excessive pressure is applied to the hair shaft when collecting samples from patients with *monilethrix*, woolly hair, etc.[17–19]

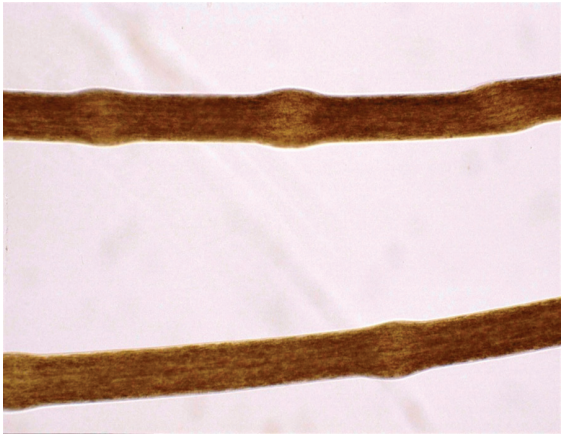

Figure 4.4 **There are round nodules without hair shaft narrowing.**

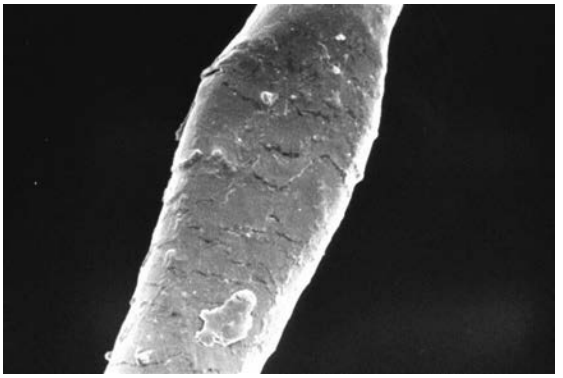

Figure 4.5 **Hair shaft flattening is observed with scanning electron microscopy (SEM).**

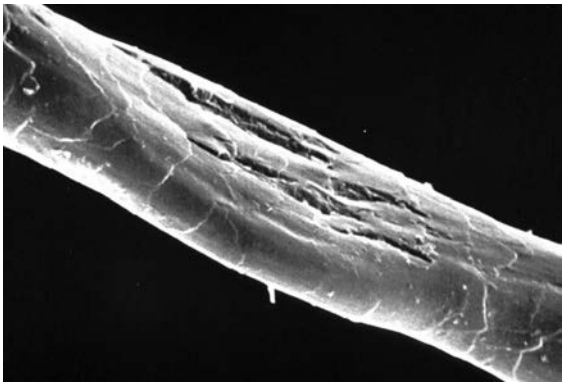

Figure 4.7 **Detail of Figure 4.6 under the SEM.**

(Figure 4.6). The same artifact is seen when the hair shaft is pressed between two slides (Figure 4.7).

Pili torti

This is a braided hair with periodic angles about its longitudinal axis. It is an AD/AR defect that may be found isolated or associated with other diseases such as Beare, Bazex, Crandall, and Björnstad syndromes, and type 2 congenital pachionychia. Atypical *pili torti* has also been observed associated with Menkes' syndrome (kinky hair) or other hair dysplasias such as *pili canaliculi* and woolly hair.[4,20] Hair appears unusually bright due to light reflection, and hypotrichosis may be observed due to an oblique fracture of the hair shaft (*trichoclasis*). Acquired and sporadic types are also recognized.[21,22]

Genetics. Mutation of *BSC1L* (Cr 2q34–36, 2q33) is responsible for the malfunctioning of ATPase that is involved in mitochondrial complex III synthesis, a situation that leads to oxygen reactive species that damage ear and hair follicle sensitive cells.[23] At least this is the case in Björnstad syndrome (AD), in which neurosensorial deafness and *pili torti* are observed.[24–27] More recently this gene has been identified in 2Mb region between *D2S2210* and *D2S2244*.

In those cases associated with type 2 congenital pachionychia, a structural alteration of keratin 17 has been observed.[28] Mutation of the *ST14* gene (Cr 11q24.3-q.25) that encodes a protease (type II transmembrane serine protease matriptase) has been identified in cases of *pili torti* associated with hypotrichosis and ichthyosis.[29] When associated with congenital hypotrichosis and juvenile macular dystrophy mutation has been identified in 16q22.1.[30,31] Other mutations have also been identified in *CDH3*.

Clinical diagnosis. Patients usually have much hair which appears irregularly bright like sequins, depending on incidence of light (Figure 4.8). It may be associated with localized hypotrichosis.

Optical microscopy. Braided hair with regular periodic angles is observed (Figure 4.9).

Electron microscopy. Images are similar to those observed in optical microscopy. Additionally, cuticle defects are found where steep angles occur.

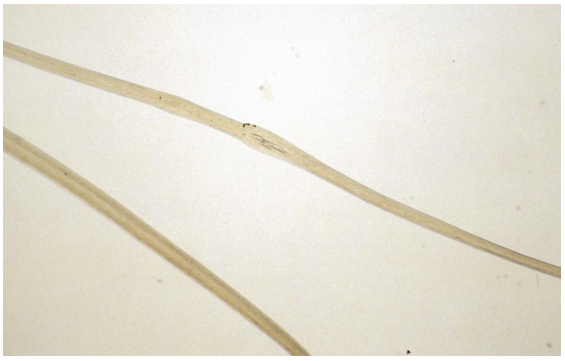

Figure 4.6 **Artifact occurs in dysplastic hair due to excessive pressure when removing it with fingers or forceps/tweezers.**

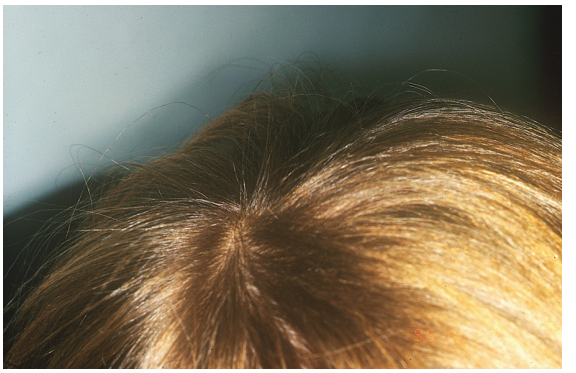

Figure 4.8 **Abundant hairs with variable bright areas appearing like sequins on *pili torti*.**

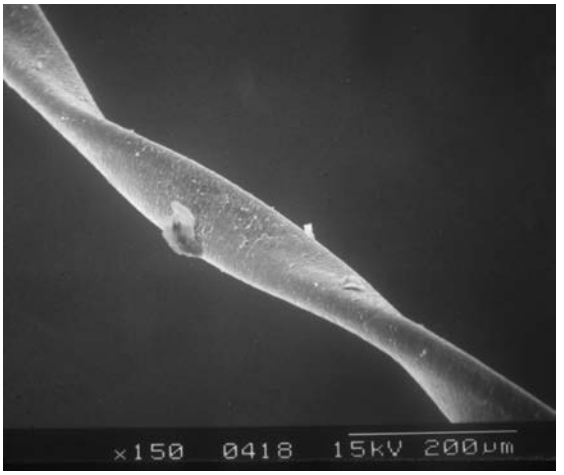

Figure 4.9 **Braided hair with cuticle defects are observed.**

Trichoscopy. A flattened hair shaft with turns at regular intervals is observed. In some cases the defect is restricted only to a segment of the hair shaft.[14] These findings are more easily observed at X70.

Biopsy. The same defect is observed intrafollicularly.

Associated conditions. Pili torti may be associated with nail dystrophy, ocular and teeth defects, follicular hyperkeratosis, and mental retardation.

Menkes, syndrome (kinky hair)

Th s is a recessive, sex-linked hereditary trait due to an alteration of the intracellular copper use and transfer, a condition that leads to intestinal malabsorption of this metal and consequently to a low level of copper and ceruloplasmin in plasma and organs (brain, liver, bone, elastin, hair, and skin). Th s syndrome is complex and involves neurological manifestations associated with hypothermia, delay in psychomotor development, limbs palsy, deafness, dwarfism, hernias, etc.[32–34] Affected children have distinctive facial features ("pudgy face," "partridge face"), scarce, fi e, brittle, and light hair. Death takes place soon due to neurological complications. We reported a case of a newborn with Menkes syndrome (MS) and transitory neonatal erythroderma.[35]

Genetics. Gene *ATP7A* encodes a transmembrane protein that controls cellular exit of copper. A mutation of this gene is responsible for MS, among other conditions. The gene is located in chromosomes X (Xq21.1), 4, 9 (9q31–q32), 14, and 18 (18.26.0 cM).[36–39]

Clinical diagnosis. Characteristically, it is a newborn with a partridge profile of the face, convulsions, and fine, scarce, brittle, and light hair (Figure 4.10).

Optical microscopy. Kinky or polydysplastic hair displays atypical irregular *pili torti*, monilethrix, and/or trichorrhexis nodosa.

Electron microscopy. Images are similar to those observed under optical microscopy (Figure 4.11). Defects

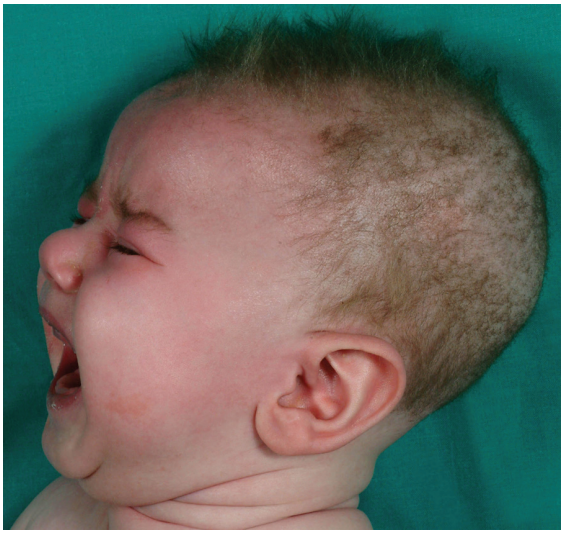

Figure 4.10 **Characteristic partridge face in a child with Menkes' syndrome. (From Galve J et al. *Pediatrics*. 2012;130:239–242. With permission.)**

of the hair cuticle are also observed, especially cuticle cells with saw aspect.

X-ray microanalysis. Low copper and sulfur content has been reported.

Trichoscopy. Hair diameter is variable. Some segments are narrow, while others look irregularly flat and twisted around the hair axis (atypical *pili torti*), a condition that may be like monilethrix. Frequently, irregular or atypical trichorrhexis may be found.

Trichorrhexis invaginata (Netherton disease)

Trichorrhexis invaginata includes both a ballooning distortion of the hair shaft as well as a chaliced deformation of the proximal hair shaft. This characteristic alteration gives the hair shaft a bamboo cane aspect; therefore, this hair dysplasia is also known as "bamboo hair," a specific hair anomaly that is considered a marker for Netherton disease.

Netherton syndrome is an autosomal recessive genodermatosis that is more frequently observed in females and may be associated with *trichorrhexis invaginata*, atopy, *ichthyosis linearis circumflexa*, *erythroderma ichthyosiformis,* and *ichthyosis vulgaris.*[4,40–42]

Genetics. Various gene mutations have been reported: kallikrein 5 (19q13.33)[43] and 7 (19q13.41), corneodesmosin (6p21.3),[44] desmochollin 1 and desmoglein 1 (18q12.1),[45] transglutaminase 1 (14q11.2) and 3 (20q11.2),[46] filaggrin (1q21), serine peptidase inhibitor (chromosomes 5 and 18, 21,5 cM), SPINK5 that encodes LEKTI a serine protease inhibitor (5q.32), and NETS (5q.32).[47,48]

Clinical diagnosis. Characteristically, the affected individual is a female with *ichthyosis linearis circumflexa* (plaques with doubled squamous border), atopy,

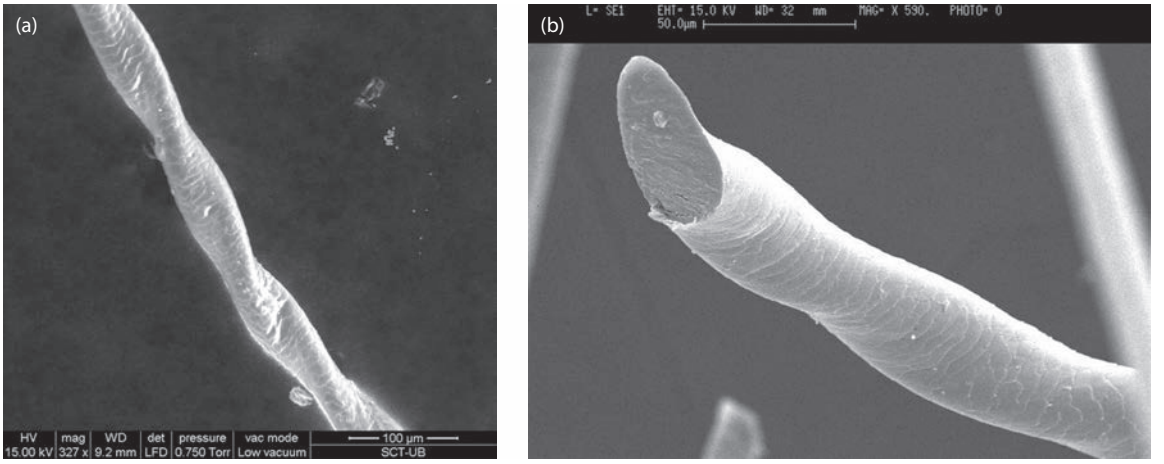

Figure 4.11 **(a,b) Atypical *pili torti* as seen under the SEM.**

and diffuse hypotrichosis (scarce and brittle hair). Other associated conditions are *ichthyosis vulgaris* and *congenital erythroderma ichthyosiformis*. Trichothiodystrophy may also be associated with ichthyosis, a condition that should be ruled out.

Optical microscopy. Bamboo hair or trichorrhexis invaginata is a typical image: the base of the hair shaft is chaliced shaped while the rest of the hair shaft shows a ballooning deformity. Eyebrows and eyelashes may also be affected.

Electron microscopy. The image is similar to that observed by the optical microscope (Figure 4.12). Hair shaft distal end may also appear as a golf tee due to hair fracture at the knot of trichorrhexis invaginata.

Trichoscopy Hairs are fractured at the nodule or knot where the shaft appears as a bamboo cane. The typical aspect includes a chalice shape of the proximal end and a ballooning distortion of the rest of the hair shaft. The distal end of the hair shaft shows a golf tee aspect due to local fracture.[49,50]

Trichothiodystrophy

Trichothiodystrophy is a complex syndrome due to a low content of sulfured compounds in the hair that leads to a specific hair dysplasia ("trichodystrofic hair")[1,4,51] in association with other clinical findings such as a delay in psychomotor development, ichthyosis, onychodystrophy, microdolichocephalia, photosensitivity, among other defects.[52,53] There are some variations of this syndrome: BIDS, IBIDS, PIBIDS, SIBIDS, ONMRS, or syndromes of Pollitt, Tay, and Sabinas, and Amish brittle hair.[54,55]

Genetics. Mutations of *TTD, ERCC2, C7orf11, ERCC3, GTF2H5, XPC,* and *GTF2H4* genes have been reported which were localized in 19q13.2-q13.3, 19q13.3, 7p14.1, 2q21, 6q25.3, 3p25, and 6p21.3, respectively.[56–61]

Clinical diagnosis. The affected individual is a newborn with congenital ichthyosis, scarce, short, and brittle hair,

Figure 4.12 **Trichorrhexis invaginata (Netherton disease) with "bamboo hair." Proximal dilatation of the hair shaft is characteristic, with a chalice-shape distortion and a distal ballooning alteration.**

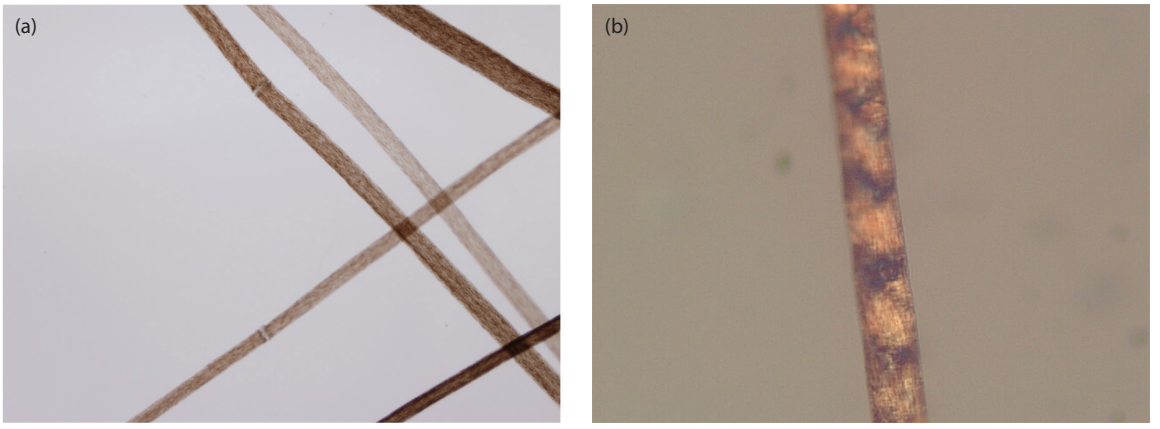

Figure 4.13 **(a) Flat hair with a typical transverse fracture. (b) Spotted and tiger-like hair surface.**

characteristic facial features, microdolichocephalia, and pleasant attitude. Other clinical findings may include mental retardation, growth delay, onychodystrophy (nail striae), and photosensitivity.[52]

Optical microscopy. Flat hair appears with typical transverse and clean transversal fractures (trichoschisis) (Figure 4.13a).

Polarized light. Alternating light and dark bands in the hair are observed, with a typical spotted tiger-like surface (Figure 4.13b).

Scanning electron microscopy. Completely rigid flat hairs like tapes are observed. Trichoschisis with a clean fracture is pathognomonic. The hair surface shows longitudinal crests and cuticle defects (Figure 4.14).

X-rays microanalysis. Sulfur content is lower than 50%.

Hair amino acid chromatography. Sulfured amino acids are clearly lowered.

Trichoscopy. Dermoscopy is not characteristic except for the trichoschisis.[62] This hair shaft may show a weaving contour and nonhomogenous structures appearing as grains of sand, alternating dark and light bands, and spotted tiger-like surface.

Trichonodosis

This is a frequent but rarely diagnosed hair dysplasia in which true knots are observed along the hair shaft. It may be suspected when the hair shaft shows an angle and changes abruptly its direction.[4,63,64] This condition is more frequently observed in individuals with curly hair in association with local trauma, scraping maneuvers, and ticks.[65] It may be found in the axillae and genitalia in association with pediculosis and acarophobia. It is not yet completely understood how double or even more complex knots are originated.

Clinical diagnosis. It usually occurs as an isolated finding. Suspicious arises when a hair changes abruptly its direction due to a true knot.

Optical microscopy. A simple, double, or even a complex true knot ("tie knot") is observed (Figure 4.15).

Scanning electron microscopy. Similar images to those observed by optical microscopy are seen. Amplification may reveal cuticle defects in the true knot area (Figure 4.16).

Trichoscopy. A simple, double or complex true knot is observed. Sometimes a "tie knot" or a "sailor knot" is observed in dermoscopy.

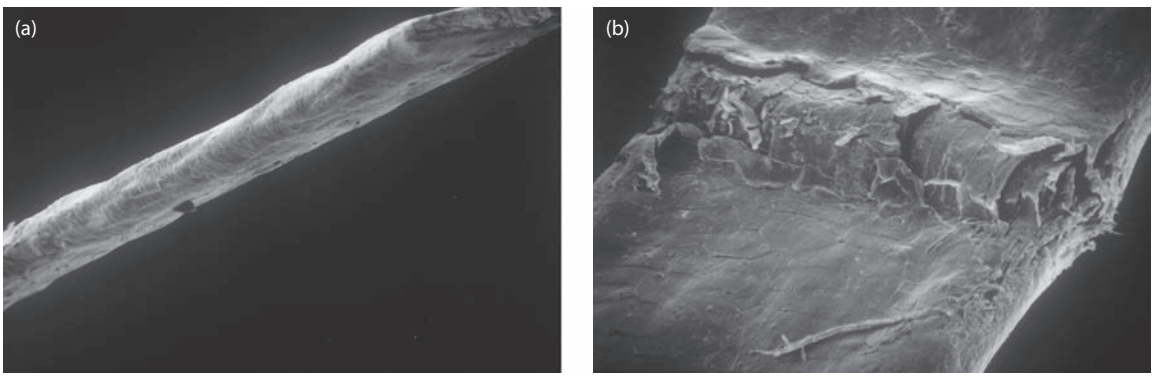

Figure 4.14 **(a) Flat hair like a tape. (b) Inicial trichoschisis at the SEM.**