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Study regarding the microscopic aspects of pilo-sebaceous units after antiandrogen treatment in hirsute women

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Abstract

Aim: To analyze the morphological data of pilo-sebaceous units in hirsute women before and 12 months after the antiandrogen treatment with Cyproterone acetate (CPA) 100 mg/day. *Materials and Methods*: Fourteen female patients with idiopathic hirsutism that followed an antiandrogen treatment with CPA were biopsied from the androgen-dependent area of the chin before and 12 months after the treatment. Routine sections were stained with Hematoxylin–Eosin, Masson, Van Gieson, Sirius red and picric-indigocarmine, while additional sections were immunostained for S100 protein and vimentin. Electron microscopy was performed in two cases with Langerhans cell hyperplasia. *Results*: On biopsies-stained sections, an increased number of hair follicles, the deeper part of the epithelial sheath of the hair follicle with epithelial buds, hyperplasia of sebaceous glands, and no inflammatory infiltrate were noticed. Langerhans cells identified with S100 protein and vimentin were normal in terms of numbers and distribution. After the administration of the treatment, atrophy of the pilo-sebaceous units was visible in nine (64.2%) cases, while inflammatory infiltrate and cells included in the vacuoles of the basal layer of the epidermis became apparent. In six of the cases treated with antiandrogens, a marked hyperplasia of Langerhans cells was noticed. In conclusion, the benefit of antiandrogen treatments is supported by atrophy of the hair follicle and the sebaceous glands. The activation of Langerhans cells associated with inflammatory infiltrate in the dermis and hair follicles could be considered as a local consequence of the involution process of hair follicles after the administration of the treatment.

Keywords: hirsutism, hair follicle, S100 protein, vimentin, Langerhans cell.

Introduction

Hirsutism in women may be defined as a manifestation of hyperandrogenism and/or the hyper-receptivity of the hair follicle in androgens, where vellus hair types are transformed into excessively thick, terminal hair types in androgen-dependent areas [1–4]. Vellus hairs are soft, thin, usually non-pigmented hairs, which from a histological point of view are non-medullated and have a diameter that reaches up to 0.03 mm [5]. Terminal (coarse) hairs are medullated, with a medulla that looks like an inner pocket area consisting of collapsed "proteins" that are not very well known [6].

In the process of hair growth regulation, various systemic and local factors and cytokines act directly and indirectly on the dermal papilla, as well as on outer and inner root sheaths or "bulge" areas [7, 8]. The androgenous hormones that stimulate pilosity activate the dermal cells of the papilla through androgen receptors (AR) [9–11].

Cyproterone acetate (CPA) functions as an antiadrogen by acting on the intracellular androgen receptor, and as an antigonadotropic agent by reducing the circulating level of the androgens. Its effect on pilo-sebaceous structures lays in the transformation of mature hairs into immature, vellus-type hairs, and is directly proportional to the duration of the antiandrogen treatment [12, 13].

Like in other instances, the therapy may induce a reaction of the local immune system. Therefore, the first cells that react are the antigen-presenting cells of the epidermis: the Langerhans cells.

Paul Langerhans first discovered dendritic cells in the mid-layer of the epidermis by using the gold chloride staining method. Later on, it was demonstrated that the Langerhans cell processes that present the antigen contain specific granules in the cytoplasm, sending long cytoplasm processes between keratinocytes [14]. Langerhans cells represent 3 to 8% of the cell population of the epidermis, and some of them are positive for vimentin. The immuno-reaction with anti-vimentin has limited specificity. It is assumed that almost all activated Langerhans cells express S100 protein. In spite of the fact that it has low specificity, S100 protein is highly sensitive.

To date, there have been little data published about the structure and morphological and immunohistochemical involution changes of the hair follicle following systemic antiandrogen treatment on hirsutism.

A recent study revealed that a trophic factor of the nervous system called galanin, which inhibits human hair growth by shortening the hair growth phase of the hair follicle (anagen), could be used as a new treatment for hirsutism [15].

The purpose of this study is to analyze the morphological alterations of pilo-sebaceous units in women with hirsutism before and 12 months after the administration of the antiandrogen treatment of Cyproterone acetate 100 mg/day, and to confirm these immunohistochemical changes through electron microscopy.

Materials and Methods

A prospective study of hirsutism was conducted in the Departments of Dermatology and Endocrinology, University Emergency Hospital of Sibiu, Romania, between 2000–2002. During the course of this study, we investigated 14 female patients with idiopathic hirsutism that had been diagnosed based on clinical, hormonal and ultrasonographic investigations in order to confirm the etiology of hyperandrogenia. The age of the patients ranged from 16 to 40 years, and the degree of hirsutism in the Ferriman–Galway score had an average of 10±3 points. A treatment with Cyproterone acetate (Androcur®) 100 mg/day associated with oral contraceptives was administrated during the course of 12 months, after obtaining the informal consent of the patients. Biopsies were taken from the androgen-dependent areas of the skin (chin) before and after the 12-month treatment with Cyproterone acetate. Biopsy fragments were processed by the classical method of paraffin embedding. The sections were stained using the standard Hematoxylin–Eosin (HE) method, Van Gieson, Masson's staining, Sirius red and picric-indigocarmine. Additional sections were immunostained by S100 protein and vimentin. Immunohistochemistry was performed with the help of a LSAB2 system, and the final reaction product was visualized through 3,3'-diaminobenzidine dihydrochloride. Electron microscopy was also performed in two cases with Langerhans cell hyperplasia, using the technique of Reynolds (LEO906 electron microscope, Zeiss Leica).

Results

On HE-stained sections, biopsies taken from the patients before the treatment showed no significant changes in the architecture of the skin. An increased number of hair follicles, hyperplasia of sebaceous glands that contain many reserve cells (Figure 1), were noted. The deeper part of the epithelial sheath of the hair follicle showed one or more epithelial buds, proliferating toward the surrounding connective tissue (Figure 2). Neither inflammatory infiltrate nor other pathological aspects of the biopsies specimen were noticed.

On Sirius red and picric-indigocarmine stained sections, hair follicles with very well defined medulla, where all sheaths, sebaceous glands and arrector pili muscle were present, could be observed (Figure 3). In Van Gieson stained sections, hair follicle with connective tissue sheath, Huxley's layer, cuticle of the root inner sheath, the medulla and the hair cortex were observed (Figure 4).
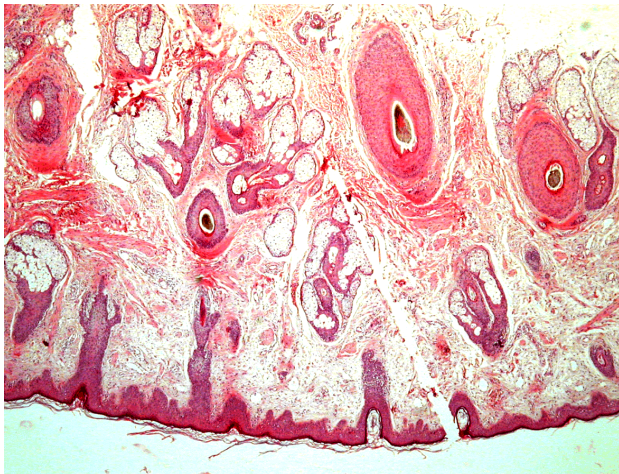

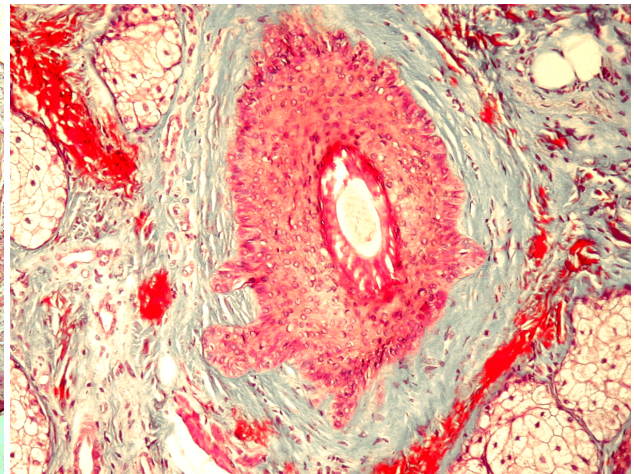**Figure 1 –** *The general aspect of the skin in patient with untreated hirsutism. HE staining, ×40.*

Figure 2 – *Hair follicle. Note the budding of the epithelial sheath. Masson's staining, ×100.*
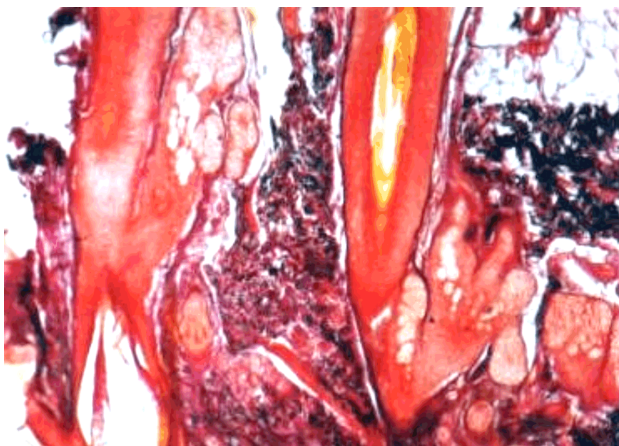

Figure 3 – *Microscopic aspect of hair follicles before the treatment. Sirius red and picric-indigocarmine, ×40.*
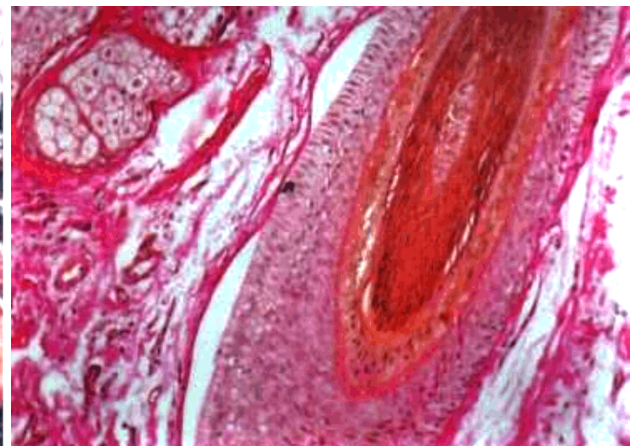

Figure 4 – *Normal hair follicle with all layers, and sebaceous glands before the antiandrogen treatment. Van Gieson staining, ×100.*

After 12 months of treatment with Cyproterone acetate 100 mg/day, the following pathological changes in the morphological aspects of the hair follicles from the androgen-dependent areas of the chin in hirsute women were found: atrophy of the pilo-sebaceous units was present in nine (64.2%) cases, inflammatory infiltrate was present in all cases, granuloma with giant multinucleated cells was present in one case, and cells included in the vacuoles of the basal layer of the epidermis were identified in four cases. In only one case, the inflammatory infiltrate invaded the epithelial component of the hair follicle.

The most common pathological changes showed hair follicles and sebaceous glands in an atrophic stage, with the latter lacking reserve cells; some of the follicles were in an advanced stage of atrophy, with only few rows of epithelial cells still visible, and were surrounded by hyaline condensation, without sebaceous glands; the epithelial cells of the sheath presented a clearly defined cytoplasm with hyperchrome nuclei (Figure 5).

From the histopathological point of view, hair follicles became thinner in most cases, since they lacked medulla. Other follicles had air areas (empty spaces) inside the medulla, beginning to present atrophic sebaceous glands.

Among our most frequent findings were hair follicles with hair bulb and hair matrix, which remained in an incipient stage, presenting a rudimentary aspect and partial keratinized cuticles. Other hair follicles presented a hair shaft-like aspect at the level of the dermis, with a keratinized cytoplasm of the medulla or a root sheath that could not be seen in all hair follicles. Moreover, we found that hair follicles with a column-like aspect presented as mass cells consisted of incipient changes in the formation of the matrix and the hair bulbs and contrasted with mature sebaceous glands. In some hair follicle fragments, the dermal papilla in the mesenchymal tissue was not observed. In most cases, the medulla presented cells without nuclei or was entirely absent. All the others layers were hardly defined, presenting a homogeneous aspect between the connective tissue sheath and the cuticle (Figure 6).

Another aspect of hair follicles with intensive keratinization processes in the proximity of the epidermis made it clear that the hair did not penetrate the epidermis, remaining as a rudimentary follicle in its proximity. Furthermore, some of these follicles and bulbs appeared to be extensions of the epidermis' basal layer (Figure 7). In other sections of the hair follicle, two main aspects were noticed: the first consisted of an immature sheath structure, while the other demonstrated an ageing process characterized by empty spaces inside the medulla. Rudimentary hair follicles presented a process of involution and keratinization in all the layers, with an evident transformation tendency in the globular corneum (Figure 8).

A transversal section of the hair follicle revealed the keratinization of the medulla and a fibrillar structure of the keratin, conveying a denaturated aspect to the hair follicles; trichohyaline had been transformed into keratin fibrils with intensive cuticle keratinization (normally, the keratinization process appears much later on at this stage).

In others sections, the medulla had been replaced by a series of air areas (vesicles, or empty spaces). In this case, an incipient concentric intramedullary keratinization process became visible. The annexed structures were hardly differentiated. An alteration of the development of the hair follicles in the early stages of the sheath and matrix formation was visible. Rudimentary hair follicles appeared in the form of a corneum cyst with parakeratotic structures and degenerated central areas. Other aspects of the involution of the hair follicles showed the ill-defined limits between sheath layers, with only few atrophic sebaceous glands in proximity.

The cortex of the hair follicle that became thinner presented degenerated cells, while the sheath layers were not clearly defined. Some of cortex cells had been replaced by air bubbles (small empty spaces), defining an aging process that was most visible in elderly patients with disintegrated hair shaft. Another feature of this process was the lack of medulla. In other hair follicles, it was observed that the cortex and the medulla either displayed a fibrillar, almost homogeneous structure, or simply lacked the medulla and the sebaceous glands altogether. The diameter of the hair follicles was reduced significantly to 30 μm (0.03 mm). Moreover, sebaceous glands were in a disintegration process characterized by an ill-defined contour appearing as adipocyte-like cells; some of the sebaceous glands had cells disintegrating from the central zone into a lipidic mass; the content stagnated because of the lack of contraction or the atrophy of the arrector pili muscle. In some sections, a rudimentary hair follicle that was in the late stages of atrophy appeared, whose cortex cells lacked nuclei and were in state of central hyperkeratinization, with only concentric fibrillar structures pointing to the initial follicle (Figure 9).

In Masson-stained sections in our hirsute patients after antiandrogen treatment, we found the following pathological changes: inflammatory infiltrate in the epithelial component of the hair follicle was present in all cases; granuloma with giant multinucleated cells was present in one case; apoptotic cells of the epithelial component of the hair follicle were present in five cases; many cells included vacuoles in the basal layer of the epidermis (intraepithelial lymphocytes). In only one case, the inflammatory infiltrate invaded the epithelial component of the hair follicle. The apoptotic cells of the epithelial component of the hair follicle showing acido-philic cytoplasm had separated from other epithelial components, presenting a hyperchromic and deformed nucleus (Figure 10).

Langerhans cells were found in large numbers in six cases after the treatment. They were distributed on all levels of the epidermis. Anti-S100 proteins were identified mainly in dendritic cells located within the epidermis, whereas vimentin was positive predominantly in dendritic cells located in the basal layer and the junction between the epidermis and dermis, as well as in the epithelial component of the hair follicle (Figure 11). The main cytoplasmic processes had extended toward the dermis, and in rare cases, thin processes were noticed between keratinocytes. Dendritic S100-positive cells where clearly found in the dermis, mainly in areas with chronic infiltrate (Figure 12).

Two out of six cases that presented a high number of Langerhans cells were selected for electron microscopy.

A selection of specific fields was performed on ultrathin sections. Criteria used to differentiate Langerhans cells from other cells with electron-clear cytoplasm were: indented nucleus, the presence of nucleolus, lysosomes and multivacuolated bodies in the cytoplasm and the absence of desmosomes. Long-branched cytoplasmic processes were observed between keratinocytes and toward the dermis. Finally, we investigated the specific cytoplasmic granules described by Birbeck. In both cases,

Langerhans cells were found in the middle of the epidermis, as well as at the junction between the epidermis and the dermis (Figure 14). In one case, only typical rode-shaped granules were noticed. In the other case, both rode-shaped and racquet-shaped granules were found. The presence of dendritic cells containing Birbeck granules was noticed in the connective tissue, where the cells were surrounded by lymphocytes.
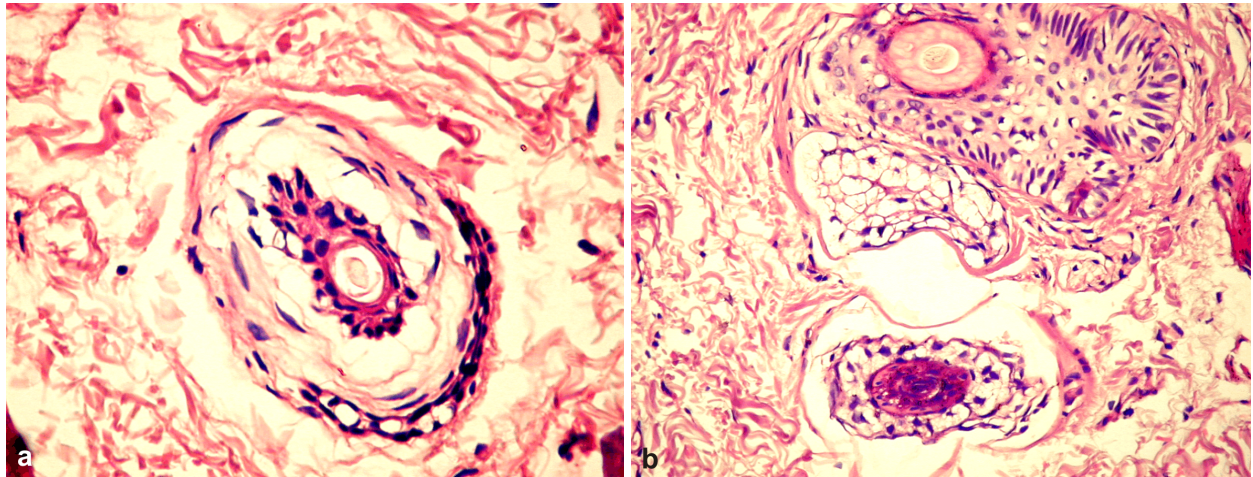
Figure 5 – *Atrophy of the hair follicle. Only some small sebaceous cells are evident in the lower right part (a). Partial atrophy of the hair follicle and sebaceous gland that lacks reserve cells (b). HE staining: (a) ×200; (b) ×100.*
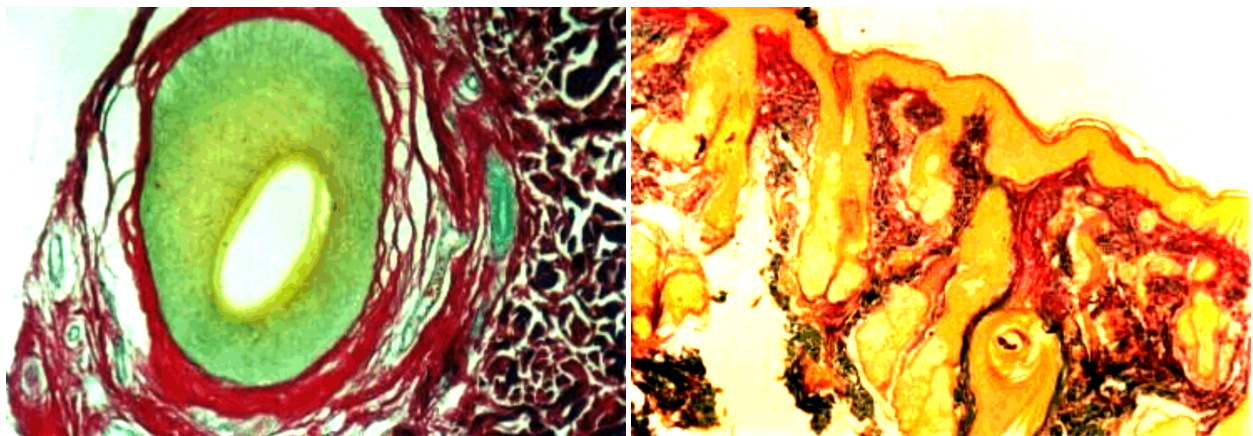

Figure 6 – *The microscopic aspect of hair follicle with homogeneous aspect after treatment. Van Gieson staining, ×200.*

Figure 7 – *Histopathological aspect of thin short hair follicles lacking the upper part of the sheath after the treatment with CPA. Sirius red and picric acid, ×50.*
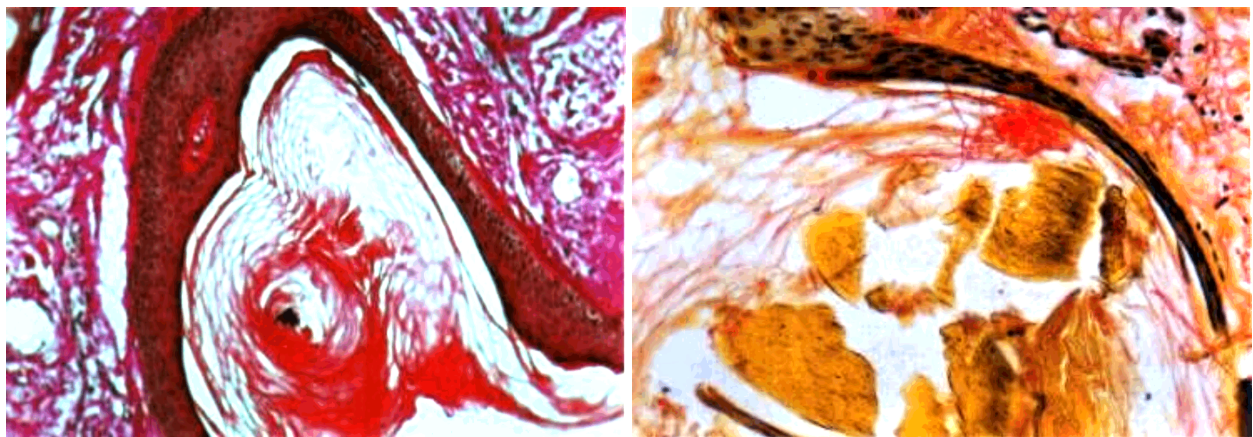

Figure 8 – *Microscopic aspects of a rudimentary hair follicle with a tendency towards becoming a globular corneum. Sirius red and picric-indigocarmine, ×200.*

Figure 9 – *Histopathological aspect of a rudimentary hair follicle with central keratinization. Van Gieson staining, ×100.*
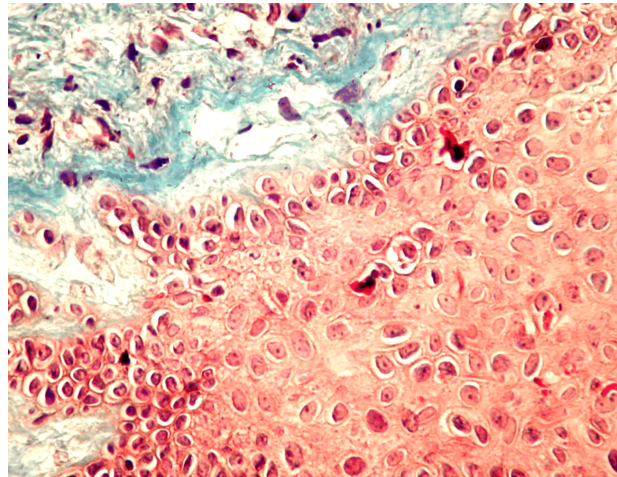
Figure 10 – *Microscopic aspect of a hair follicle with apoptotic cells of the epithelial component of the hair follicle. Masson's staining, ×200.*
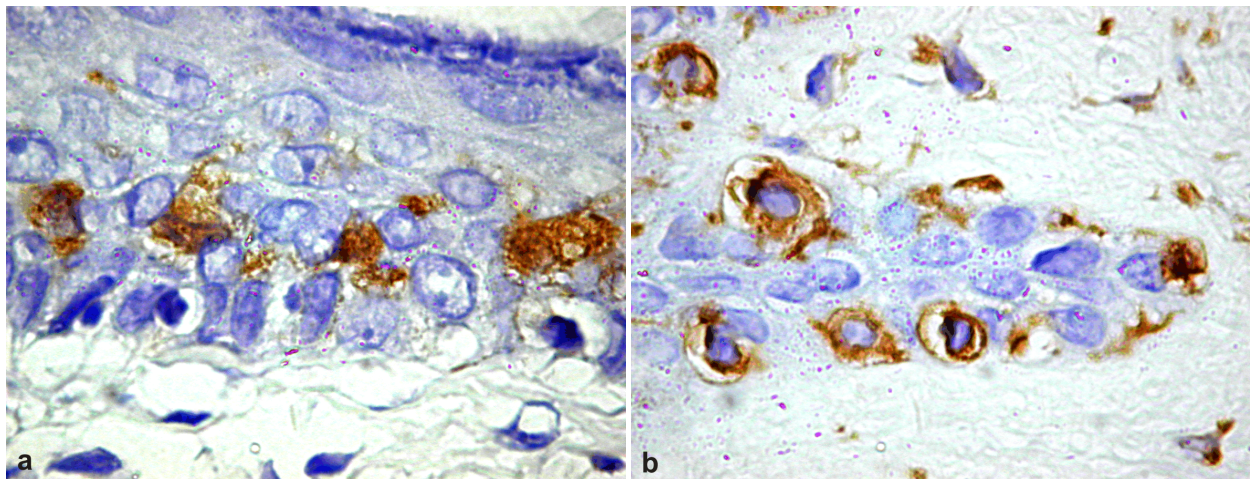

Figure 11 – *Langerhans cells located in the middle and basal layers of the epidermis, identified with anti-S100 protein (a, ×400), and in the basal layer, identified with vimentin (b, ×400).*
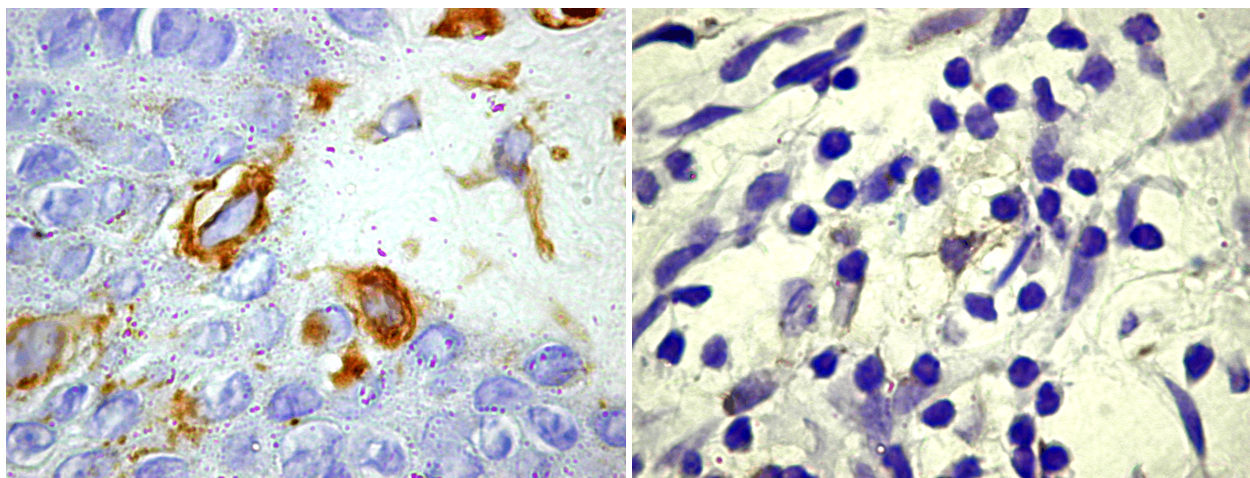

Figure 12 – *Vimentin-positive cells with dendritic feature in the basal layer of the epidermis and upper dermis (×900).*

Figure 13 – *S100-positive cell with thin cytoplasmic processes in the chronic inflammatory infiltrate (×400).*
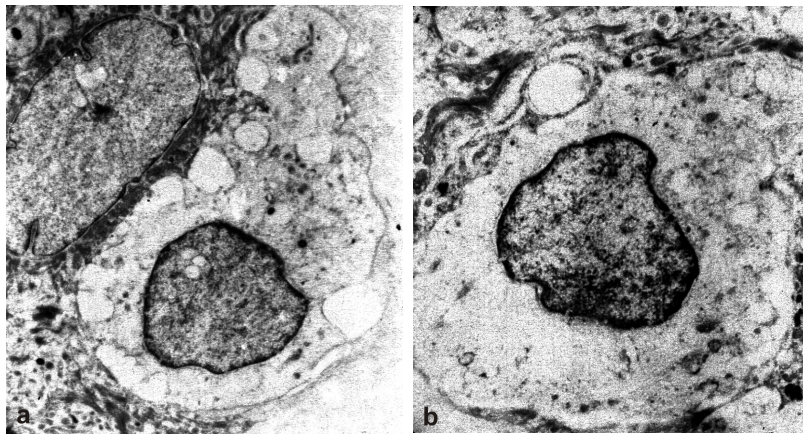
Figure 14 – *Electron microscopy: Langerhans cell with branched cytoplasmic processes at the dermo–epidermal junction (inset: rode-shaped granule) (a, ×8000). Langerhans cell in the dermis (b, ×8000).*

⊡ Discussion

In female patients with hirsutism where usual and special staining methods were used (Hematoxylin–Eosin, Van Gieson, Sirius red and picric-indigocarmine), a normal aspect of the hair follicle in androgen-dependent areas was observed before the treatment with Cyproterone acetate, displaying visible medulla, sebaceous glands and arrector pili muscles.

The involution of the hair follicle and the annexes under treatment with Cyproterone acetate 100 mg/day for the duration of 12 months consisted of manifestations of rudimentary, immature and non-medullated hairs of the vellus type. The changes were: the infringement of the hair follicle development in incipient stages of the sheath and matrix formation, and the formation of air areas (empty spaces) inside the medulla. In some cases, the amplification of the pilo-infundibulum plagued with keratosis cysts took place. Moreover, an inversed pilo-keratosis was noticed through the profound invagination of certain basal cells that corresponded to the rudimentary hair follicles. After the treatment, the diameter of the hair follicle was reduced to 0.03 mm, a result that is similar to other data available in literature [5]. Furthermore, sebaceous elements were attenuated and the erector pili muscles were fragmented in a way that deterred them from contributing to the verticalization of hair follicles.

Sebaceous dysfunctions were confirmed through the identification of larger quantities of lipids in rarefied sebaceous elements. Furthermore, our research revealed severe degenerations of the hair pillar, with pseudo and microcysts containing rudimentary hair follicles.

Hair keratinization, which is normally produced differently for each individual hair sheath, was produced abruptly after the administration of the treatment in our case, jumping ahead to the "hard" keratinization stage. In particular, the Huxley layer was keratinized intensely, along with those structures that are normally keratinized among the first. A discrepancy between the development of mature sebaceous glands and hair follicles that were still in an incipient formation stage was noted. The factors that regulate the hair's growing cycle, as well as cellular divisions at a pilo-matrix level are: steroid hormones, dermo–epidermal interactions and the immune system [7, 8].

Androgens are the main regulatory hormones of hair growth [9]. Androgens may act on hairs follicles directly and/or independently on their serum levels, producing an intracrine or local effect, especially in idiopathic hirsutism [6]. Androgens also increase the peripheral activity of

5α-reductase and, consequently, the effect of androgens on hair follicles [16, 17].

Alongside androgens, the control of hair growth and hair differentiation is established through local and circulating growth factors as transforming growth factor (TGF) and epidermal growth factor (EGF), stem cell factor (SCF) and vascular endothelial growth factor (VEGF). The emissions of some factors are influenced by *in vitro* androgens [18, 19], which function, at least in part, through the induction of matrix metalloproteinases (MMPs). Immunohistochemistry localized MMP-9 in the inferior side of the internal epithelial root sheath, in the Henle layer [20].

These factors influence the activity of the 5α-reductase enzyme (5α-RA) of both types [21–23]. This enzyme can be localized in the outer root sheath of the hair follicle, with less expression in the dermal papilla [24].

Immunohistochemical studies [25] investigated the manifestation of cytokeratin K19 – a marker of hair follicle stem cells, since keratinocytes are similar to multipotent stem cells [26]. Similarly, immunohistochemical studies performed on our patients after systemic antiandrogen therapy have highlighted inflammatory infiltrate that contained both lymphocytes and granulocytes in the papillary, perivascular and perifollicular dermis. Immuno-staining with vimentin and S100 protein revealed the presence of dendritic-like cells in the epithelial tissue of the hair follicles.

Langerhans cells are mobile, since they are able to migrate within the dermis, participating to the synthesis of prostaglandins, the interferon, lysozymes and certain lymphokines [14, 27, 28]. Before the administration of the antiandrogen treatment, the Langerhans cells that had been identified with S100 protein and anti-vimentin were localized in the epidermis, demonstrating (normal) average values in terms of number and distribution. In these instances, positive cells were not observed at the dermo–epidermal junction or the papillary dermis. After the antiandrogen treatment, Langerhans cells became more numerous. The anti-S100 protein succeeded to identify most Langerhans cells localized in the epidermis, while anti-vimentin tested positive for dendritic cells in the basal layer of the epidermis, in dermo–epidermal junctions, in the superior part of the papillary dermis and the epithelial tissue of the hair follicle. S100-positive dendritic cells were present at the dermis level, predominantly in areas with chronic inflammatory infiltrate.

At the core of this study was the issue of the high

number of dendritic cells, as well as the question of whether Langerhans cells found in dermo–epidermal junctions were truly representative of migratory cells that followed the path from epidermis to dermis or *vice versa*. Electron microscopy revealed long-branched cytoplasmic extensions, which were either present among keratinocytes and towards the dermis or specific rode-shaped or racquet-shaped Birbeck granules. Similarly, the presence of dendritic cells containing Birbeck granules was observed within the conjunctive tissue, and was encircled by lymphocytes.

The existing literature does not describe such aspects. For this reason, the results obtained through the S100 immunostaining method should be correlated to the anti-androgen treatment, since it is our opinion that hirsutism itself cannot induce such aspects. At this moment, such high numbers could support the hypothesis that reactive mechanisms are triggered by local involution processes of the hair follicles.

⊟ Conclusions

The benefit of the antiandrogenic treatment is supported by the atrophy of the hair follicle and the sebaceous glands in 64.2% of the cases. The development of the hair follicles was deterred in the incipient stages of the formation of the matrix and hair shafts, with occurrences of non-medullated vellus hair, as well as the formation of empty air spaces in the medulla and the cortex. The morphological and immunohistochemical study of the skin of 14 patients with idiopathic hirsutism revealed significant changes in the number and distribution of Langerhans cells in hirsute women treated with antiandrogens. On the other hand, activation of Langerhans cells associated with inflammatory infiltrate in the dermis and hair follicles could be considered as a reactive mechanism triggered by local involution processes of the hair follicles.

Conflict of interests

The authors declare that they have no conflict of interests.

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