5-Fluorouracil-Induced Reticular Hyperpigmentation

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To the Editor

5-fluorouracil, a fluorinated analogue of pyrimidine, is an antineoplastic drug used to treat tumors, especially those of the digestive tract.

Many cutaneous side effects have been described in association with this drug, including lesions similar to lupus erythematosus, outbreaks of seborrheic dermatitis, photosensitivity, folliculitis, palmar keratoderma, periungal ulceration, nail deformities (Beau lines), inflammation of actinic keratosis, palmar planter erythrodyssesthesia, and changes in pigmentation.1,2

We present the case of a patient with reticular and mottled hyperpigmentation associated with the systemic administration of 5-fluorouracil.

The patient was a 75-year-old man, with a history of high blood pressure and diabetes mellitus, diagnosed with stage III cecal carcinoma in February 2006. He underwent right hemicolectomy followed by neoadjuvant cycles of chemotherapy with 5-fluorouracil, oxaliplatin, and folinic acid. Following the fifth infusion, he reported the rapid appearance of asymptomatic pigmentation on his back and the palms of his hands. He reported no skin lesions prior to hyperpigmentation.

A physical examination revealed a brownish, macular, reticular hyperpigmentation in the lumbar region, mottled coloring on the palms of the hands, and hyperpigmentation in the lines on the hands (Figures 1 and 2).

A biopsy was taken of the reticular hyperpigmentation on the back. The histological study showed an epidermis with hyperkeratosis and increased basal pigmentation. A small amount of chronic inflammatory perivascular lymphocytic infiltrate was seen in the superficial dermis with occasional melanophages (Figure 3).

The patient continued to receive cycles of chemotherapy, with no observed increase in pigmentation, until completing the treatment after 11 infusions.

Five months after the last cycle of chemotherapy and 8 months after the appearance of the hyperpigmentation, no pigmentation was seen on the palms of the hands, and the reticular pigmentation still present on the back had decreased in intensity.

Hyperpigmentation of the skin is a side effect associated with various chemotherapy drugs including bleomycin, cyclophosphamide, etoposide, carboplatin, hydroxyurea, capecitabine, melphalan, and 5-flourouracil.3,4 This hyperpigmentation can affect the skin, mucosa, and nails. Systemic administration of 5-fluorouracil has been associated with various patterns of pigmentation, most commonly in areas exposed to sunlight. Hyperpigmentation has also been described in irradiated areas, along with diffuse and mottled pigmentation on the hands and feet, melanonychia, and pigmentation of the oral mucosa.1-3,5

Less common cases of serpiginous supravascular hyperpigmentation have been reported, where pigmentation was seen in the skin overlying the veins through which the drug was injected.6,7

The reticular or serpiginous pattern has been associated with 5-fluorouracil only in exceptional cases.1,3,9 Although the clinical presentation suggests 5-fluorouracil-induced pigmentation in this case, the phenomenon may have other causes. A similar pattern was first described in association with bleomycin9 and later with idarubicin infusion.3

Our patient was being treated with 2 antineoplastic agents (oxaliplatin and 5-fluorouracil), and we attribute the reticular pigmentation to 5-fluorouracil on the basis of cases described previously.
in the literature, even though it is an exceptional side effect. However, an association with oxaliplatin cannot be ruled out, despite the absence of published case reports.

The cause of this drug-related hyperpigmentation is unknown, although there may be a mechanism common to all the cited chemotherapy drugs. These substances could increase pigmentation by means of melanocyte-stimulating hormone or by direct stimulation of melanocytes themselves. The reaction could also be provoked by higher concentrations of the drug in areas of skin experiencing greater blood flow.

This pigmentation is clinically reminiscient of erythema ab igne, which has been related to long-term exposure to heat below the burn threshold. Such exposure to heat would cause erythema followed by postinflammatory pigmentation with this cutaneous vascular pattern.

In our patient, as in the cases described in the literature, the hyperpigmentation did not recur in later cycles, although the drug was maintained and the dosage remained unchanged. It is therefore possible that the patient presented hyperpigmentation due to local toxicity of the drug, resulting from increased blood flow to this location, as would occur, for example, with an increase in ambient temperature.

This would be interpreted as postinflammatory pigmentation of the overlying skin taking a cutaneous vascular pattern—similar to the supravenous hyperpigmentation described in association with 5-fluorouracil—due to subclinical phlebitis induced by the infusion or by localized hyperthermia. We conclude that this case of reticular hyperpigmentation was an exceptional side effect of 5-fluorouracil, even though the same symptom has also been associated with the infusion of other antineoplastic agents. We suggest it was produced by a higher concentration of the drug in areas of skin that experienced greater blood flow. It occurred as an asymptomatic and persistent cutaneous reaction that did not require any modification of the prescribed oncological treatment.

References

Imported Donovanosis in an Adolescent Girl

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To the Editor

Donovanosis or granuloma inguinale is a granulomatous, progressive, ulcerative bacterial infection caused by Calymmatobacterium granulomatis. This infection is rare in children or adolescents. However, we present the case of a 12 year-old girl seen at our hospital, after referral from the Tangiers Hospital, Morocco, with an ulcerative genital lesion that had been present for 1 year, diagnosed as squamous cell carcinoma. The patient had been raped by a family member some months before the lesions appeared. Examination

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revealed a painful ulcer 5-6 cm in diameter on the labia majora (Figure 1). Ulceration was also present in the mouth, acquired through direct sexual contact with the attacker’s genitalia (Figure 2).

Laboratory tests, serological tests for the human immunodeficiency virus, syphilis, hepatitis B and C, and routine bacteria cultures gave negative results.

The skin biopsy revealed the presence of short, thin bacteria which stained positively with Giemsa solution and which were located within the cytoplasm of the dermal macrophages, forming organisms known as Donovan bodies.

Clinical examination and biopsy findings led to a diagnosis of donovanosis.

Doxycycline 200 mg/d was prescribed, and clinical improvement in the lesion occurred in the first 7 days. Treatment was maintained for 3 months until the lesion was totally healed.

Donovanosis or granuloma inguinale is a contagious disease produced by C. granulomatis, and is mostly seen in adults aged between 30 and 50 years old in tropical or subtropical regions. The disease is commonly, but not exclusively, transmitted by sexual contact with an infected person. It is a very rare infection in children and cases in the pediatric population tend to be transmitted via the birth canal.

The clinical form tends to be characterized by localized nodules in the genital area that usually become ulcerated. Of the extragenital sites, which tend to be rare, the oral cavity is the most common as a result of the practice of oral sex. Hematogenous spread is very uncommon, and occurs almost exclusively in pregnant women.

There is no specific culture medium for C. granulomatis, as it has rarely been cultivated successfully by research laboratories. Polymerase chain reaction techniques have been developed on the basis of genetic similarity to bacteria of the Klebsiella pneumoniae and rhinoscleromatis genus, although this technique is not routine.

Differential diagnosis must be made with Behçet disease, squamous carcinoma, Crohn disease, pyoderma gangrenosum, syphilis, and canker.

Treatment with trimethoprim-sulfamethoxazole, doxycycline, or azithromycin is recommended. Antibiotics must be continued until the lesion is fully resolved.

This is the first case in Spain of a female adolescent being treated for imported donovanosis, as all previous cases had been in adults.

This new case illustrates the need for knowledge of imported diseases, which can also affect the pediatric population, given the increased immigration of recent years.

References

To the Editor

In 1999, Carlson et al. described 2 cases of a pigmented matrical neoplasm composed of matrical cells and dendritic melanocytes. The authors named this neoplasm, which was clearly distinct from pilomatricoma, melanocytic matricoma. This tumor mimics a normal anatomic process that takes place in the healthy bulb of an early anagen hair follicle.

We present a new case of melanocytic matricoma seen recently in our department. Only 10 such cases have been reported to date.1-7

The patient, a 66-year-old man with a history of hypertension, was referred to our department for evaluation of an asymptomatic lesion that had appeared on the bridge of his nose 1 year earlier. According to the patient, the lesion had appeared on normal skin and grown slowly. There was no family history of similar lesions. The patient had undergone cryosurgery in the past to treat facial actinic keratosis.

Physical examination revealed a blackish tumor with a diameter of 2 mm and clearly defined borders on the bridge of the nose. There was no evidence of any other skin lesions.

Histopathology revealed a well circumscribed pigmented tumor in the middle and deep dermis (Figure 1). The tumor was composed of a biphasic cell population formed by melanocytes (several of which were heavily pigmented) with some mitotic activity, and epithelial cells of varying size and eosinophilic cytoplasm with abrupt transition to anucleated shadow cells (Figure 2). Also visible were small areas of calcification (Figure 3).

Immunohistochemical analysis revealed that epithelial components were positive for cytokeratin AE1/AE3 and melanocytic components for human melanoma black-45 (Figure 4).

Our findings are similar to those described in all the case reports of melanocytic matricoma published to date (Table). Clinically, melanocytic matricoma lesions are a blackish color and measure less than 1 cm in diameter; they occur in elderly patients (60-80 years), mostly men, with sun-damaged skin.1-6 There has been 1 report of melanocytic matricoma on the tail of a dog.7

Histopathologic findings include pigmented nodular proliferation in the dermis composed of matrical cells, supramatrical cells, and shadow cells admixed with heavily pigmented dendritic melanocytes. Calcification and granulomatous reactions are uncommon.1-7

The small size of the lesions, their well circumscribed borders, and the lack of recurrence all suggest a benign neoplasm rather than a matricoma, despite the presence of variable cytologic atypia and frequent mitoses (characteristic of matrical cell tumors).38
It is known that hair follicles in anagen (growth phase) contain matrical and supramatrical cells as well as pigmented melanocytes that give hair its color. Mitotic activity is also common. Because melanocytes are more prominent in the early anagen phase, melanocytic matricoma is suggestive of early-stage follicular differentiation during anagen; this contrasts with pilomatricoma, which is characterized by late-stage differentiation.3-6

Clinical differential diagnosis should include pigmented basal cell carcinoma, malignant melanoma, and hemangioma. Histopathological differential diagnosis, in contrast, should include matrical carcinoma with prominent melanocytic hyperplasia, malignant melanoma, matricoma, trichoblastoma, basal cell carcinoma with matrical differentiation, and pigmented pilomatricoma.4-6

Ever since melanocytic matricoma was first described by Carlson et al,1 there has been some discussion about whether there is sufficient clinical and pathologic evidence to support the hypothesis that it is a separate entity from matricoma.9-13

It has been suggested that matrical carcinoma with prominent melanocytic hyperplasia might in fact be a malignant form of melanocytic matricoma; this variant of carcinoma is a poorly defined, multinodular tumor that penetrates deeper layers and contains mitotically active cells and areas of necrosis.8

Pilomatricoma occurs in young people as a cystic neoplasm, is firm to the touch, and is located in the deep dermis or subcutaneous tissues; it is often accompanied by calcification and granulomatous reactions.14-16 Pigmented pilomatricoma does not have prominent melanocytic hyperplasia, contrasting with the marked proliferation of pigmented dendritic melanocytes in melanocytic matricoma.16-19 The difference between these 2 entities has been likened to that between pigmented seborrheic keratosis and melanocanthoma.3,6

References
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Bilateral Congenital Triangular Alopecia Associated With Congenital Heart Disease and Renal and Genital Abnormalities

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To the Editor:

Congenital triangular alopecia, also known as temporal triangular alopecia or Brauer nevus, is a nonscarring circumscribed permanent and asymptomatic alopecia that was first described by Sabouraud in 1905. It is usually found on the frontotemporal area and affects only 1 side of the head.

Histopathology of the affected area reveals reduced hair follicle size, although hair density remains normal, with no other significant abnormalities. Diagnosis is usually clinical. Other causes of nonscarring circumscribed alopecia must be ruled out, especially alopecia areata, with which it is often confused. In the literature, there are reports of different conditions that coexist in patients with congenital triangular alopecia. We present the association between bilateral congenital triangular alopecia and a multiple malformation syndrome.

The patient was a 7-year-old boy with a history of congenital heart disease involving a perimembranous ventricular septal defect and an atrial septal defect with no hemodynamic consequences. He also had a history of left hydronephrosis, subcoronal hypospadias, Wormian bones, and recurrent bronchiolitis. The patient was referred because of the presence on the scalp of 2 areas with finer, lighter-colored hair, which his parents remembered as being there since birth. There had never been total hair loss in the area, and the patient

Figure 1. Oval alopecia plaque on the right temporal region.

Figure 2. Congenital triangular alopecia on the left frontotemporal region reaching the hairline.
had not responded to topical corticosteroids. There was no history of injury or a family history of similar processes.

Physical examination revealed 2 approximately oval areas on the temporal region. These were well delimited, 2 × 4 cm in diameter, and covered with vellus hair, with no exclamation mark hair (Figures 1 and 2).

The pull test was negative and the surface of the underlying skin was normal (no atrophy, flaking, follicular pustules, or changes in coloring).

Although there have been few published reports of congenital triangular alopecia, it is not uncommon, and some authors have reported a frequency of 0.11%. It seems to affect both sexes equally and has been reported mainly in whites, although there have also been cases among Asians and African Americans.2

Clinically, it is characterized by finer hair in a more or less triangular area with blunt angles and the base of the triangle lying towards the hairline, although it can sometimes be oval or round.3 It is usually unilateral and affects the frontals, parietotemporal area, although there have been reports of lesions in the occipital region and bilateral involvement (20%). Although it is considered congenital, it usually appears between 3 and 6 years of age, and sometimes during adolescence or adulthood. Given the variability in age at diagnosis, some authors prefer to call it temporal triangular alopecia.3

The pathogenesis of congenital triangular alopecia remains unknown and its genetic basis is unclear. Paradoxically, inheritance has been postulated.4 This would explain the sporadic nature of the process (with very few familial cases) and a limited number of members affected), its tendency to be unilateral, and its association with phacomatosis pigmentovascularis as a component of twin spotting.2 It has been associated with Down syndrome, leuconychia, sectorial iris hyperpigmentation, woolly hair nevus,5 mental retardation,6 epilepsy,6 Dandy–Walker malformation,6 LEOPARD syndrome,7 and aplasia cutis congenita. Some authors believe that developmental neurological abnormalities and phacomatosis pigmentovascularis are not simple causal associations.6,9

Histopathology reveals normal hair density—although the hair is of the vellus type and not terminal hair—and no added scarring or inflammatory abnormalities are apparent.1

Diagnosis is based on its stable nature and characteristic clinical pattern, and a histopathology study is not usually necessary. In addition to the clinical history and location, the normal appearance of the skin in the affected area is very important.2,3 Differential diagnosis should be made with other causes of nonscarring circumscribed alopecia, especially alopecia areata, which can also appear in childhood, even at birth,10 but which is associated with a positive pull test, exclamation mark hair, and completely bald areas. In addition, alopecia areata, is not static and often regresses spontaneously or after administration of intralesional or topical corticosteroids.1,10 In some cases, a histopathology study is necessary to differentiate between the 2 entities, but the result might not always be definitive. Perifollicular inflammation can be observed in alopecia areata, except for some cases of chronic alopecia areata.3

There is no effective treatment for congenital triangular alopecia and it is not usually necessary. The nature of the entity should be explained to parents so that they can avoid fruitless or harmful treatments (especially topical corticosteroids).1,2 The symptoms remain stable for life and both males and females can undergo surgical removal of the affected area. In some cases, hair has been implanted using micrografts.1

In conclusion, we present a new case of bilateral congenital triangular alopecia in a patient with multiple malformation syndrome. This may be another illustration that perhaps these associations are not casual.
Vulvar Syringoma: A Rare Cause of Vulvar Pruritus

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To the Editor:

Although vulvar syringomas are rare, they are probably underdiagnosed because most are asymptomatic lesions. However, they can give rise to vulvar pruritus that is unresponsive to conventional treatments and, if severe, may considerably affect quality of life. Consequently, such lesions should be considered in the differential diagnosis of pruritus and popular lesions of the vulva.

We describe a 78-year-old woman with a 9-year history of urinary incontinence who consulted for intermittent, nonseasonal vulvar pruritus that had started 4 years earlier. She was treated with oral antihistamines and topical corticoids, but did not improve. The physical examination showed multiple papules of 3 to 5 mm that were flesh-colored and of lichenoid appearance. Some of these papules were eroded on the surface and coalesced to form plaques on both of the labia majora (Figure). No such lesions were observed at other sites.

Contact allergy testing based on the standard Spanish panels was positive at 96 hours for the perfume blend and the black rubber blend. Biopsy of a papule showed a proliferation composed of nests and ducts of epithelial cells embedded in a stroma of collagen bundles. The ducts were lined with 2 layers of cuboid cells and some showed tadpole-like extensions. These findings were consistent with eccrine syringoma.

The lesions were treated by carbon dioxide laser, with clear improvement in both the symptoms and the lesions. After 11 months of follow-up, the patient has presented few episodes of pruritus, all less severe than before and controlled with topical corticoids.

Syringomas are a benign tumor of eccrine origin usually located in the periocular region; however, there are other, more unusual sites, such as the vulva. Simultaneous involvement of the vulvar region and extragenital areas has been described. It mainly affects women during puberty and middle age, and rarely manifests in the later years as in our case.

Syringomas are usually asymptomatic, but can cause pruritus in the vulva. On occasions, pruritus may become more severe during menstruation, pregnancy, and summertime. A review of the published cases of vulvar syringomas indicates that pruritus develops over a number of years before the definitive diagnosis, severely impacting on quality of life. Persistence of the lesions may occasionally cause venereophobia and carcinophobia.

Three clinical forms of presentation of vulvar syringomas have been described. Most commonly, they appear symmetrically on the labia majora as multiple flesh-colored or brownish papules. The other presentations are cystic lesions or lichenoid plaques, as was the case in our patient. The clinical differential diagnosis mainly considers epidermal cysts, steatocystoma multiplex, condyloma, lichen planus, and lichen simplex chronicus.

Because the appearance of vulvar syringoma is nonspecific, clinical diagnosis of this condition may be difficult. Histology is key to establishing the diagnosis and ruling out malignancy. In the case of vulvar syringoma, histology will reveal dermal proliferation composed of cells arranged in nests and ducts within a fibrous stroma. Some ducts present characteristic small, comma-shaped epithelial cell tails that resemble a tadpole. Normally, the ducts are lined with 2 rows of epithelial cells and may be filled with eosinophilic material.

In our case, the clinical symptoms, physical examination, and additional tests excluded other common causes of vulvar pruritus such as candidiasis, scabies, pediculosis, allergic contact dermatitis, psoriasis, lichen sclerosis, and atrophic lichen. Because the patient had a history of urinary incontinence, she was initially diagnosed with irritant dermatitis and associated lichen simplex chronicus, but later definitively diagnosed with syringomas after the biopsy. The presence of lichenification due to chronic scratching may mean that vulvar syringomas are hard to see and, therefore, patients may be incorrectly diagnosed with lichen simplex chronicus. Therefore, vulvar syringoma should be considered in all patients with lichen simplex chronicus who respond poorly to oral antihistamines and topical corticoids.

The treatment for vulvar syringomas is not standardized. Only a minority of patients achieve adequate control of pruritus with topical corticoids, with or without oral antihistamines. Oral tranilast, topical atropine, curettage, cryotherapy, electrosurgery, and resection are some of the treatments that have been used with variable results. One of the best therapeutic options is carbon dioxide laser treatment, which has proven to be highly effective for the relief of pruritus and for resolving the lesions safely and easily.
LETTERS TO THE EDITOR

Oncocytoma of the Lacrimal Caruncle

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To the Editor:

Oncocytomas are neoplasms that originate in the glandular and secretory epithelia.1 Histologically, the masses are composed of polyhedral cells of granular eosinophilic cytoplasm, which presents abundant mitochondria when examined ultrastructurally.1 In cutaneous presentations, the most common sites are the ocular caruncle and medial eyelid canthus.2

The incidence of neoplasm in the caruncle is around 3% of all tumor biopsies from ocular adnexa. Ostergaard3 published a Danish series spanning 25 years that included 574 biopsies of caruncular lesions, reporting an incidence of 2.8%. In another series of 466 biopsies of the caruncle reported by Pecorella,4 the incidence of oncocytoma was 2.7%. This tumor is more common among older adults and women: the average age at presentation is 73 years and 5 times more women than men are affected.4 Biologically, the tumor is benign, although malignant oncocytomas have been described.5

We describe an 82-year-old man who attended an ophthalmology clinic in Colombia for a cystic lesion that had been growing on the inner area of the left eye for 1 year and presented occasional bleeding. The physical examination revealed a rounded polypoid lesion measuring 7 mm across in the caruncle of the left eye. The lesion was highly vascularized, but there was no involvement of the skin of the palpebral fold. The mass was surgically removed.

The anatomical pathology department received a fragment of tissue partially lined with epidermis that measured 1.2 × 1.1 cm at the largest diameter. The fragment contained a strongly vascularized reddish-brown polypoid lesion of 0.7 × 0.6 cm at the cross diameter. Tissue sections with hematoxylin eosin stain showed an area of palpebral and bulbar conjunctiva corresponding to the area of the caruncle. The lamina propria contained a benign tumor of epithelial origin composed of polyhedral cells with a slightly hyperchromatic central nucleus and eosinophilic granular cytoplasm, with well-circumscribed cell borders. The cells were arranged in solid nests associated with vascular congestion and foci of microhemorrhaging (Figure 1). Periodic acid-Schiff staining revealed an intense granular acidophilic content in the cytoplasm, corresponding to the high number of mitochondria (Figure 2).

The lesion was diagnosed as an oncocytoma of the lacrimal caruncle. Oncocytoma, also known as an oncocytic tumor or oxyphilic cell adenoma, is a tumor that originates in the cells of glandular and secretory epithelia. Oncocytomas have been
described at different sites, mainly the salivary, parathyroid, adrenal, and thyroid glands, kidneys, gastrointestinal system, and ocular adnexa. The most common site in the eyes is the caruncle and the inner canthus of the eyelids, although the condition has also been reported in the lacrimal gland and conjunctiva.

Oncocytomas of the caruncle are slow-growing lesions that reach an average size of 2 to 5 mm and may be solid or cystic. The lesions are asymptomatic, but may occasionally be accompanied by an inflammatory response and become reddish. They are usually removed to establish diagnosis and for cosmetic reasons.

Histologically, oncocytomas are characterized by the presence of polyhedral cells, with abundant granular and eosinophilic cytoplasm (Figure 1). The cytoplasm stains with periodic acid-Schiff reagent and phosphotungstic acid (Figure 2). The cells show positive antibody reactions to low-molecular-weight cytokeratins; some of the tumor cells are diffusely positive for carcinoembryonic antigen. The cells are not immunoreactive to vimentin, CD68, S100 protein, or HMB-45 monoclonal antibodies. Electron microscopy has shown that the cytoplasm of these cells is occupied by large quantities of mitochondria filled with crystals.

The differential diagnosis should be established with benign masses of inflammatory origin, papilloma, dermoid and epidermoid cyst, basal cell carcinoma, angioma, and pyogenic granuloma.

Oncocytomas of the caruncle rarely recur and are classified as biologically benign, although cases of malignant oncocytoma of the eyelid, known as oncocytic carcinoma, have been reported. These oncocytomas differ from benign oncocytomas in their cellular atypia, invasive nature, and development of recurrences and metastasis. In our patient, lesions had not recurred after 6 months of clinical follow-up.

In conclusion, our literature review did not reveal any reports of this disease in Colombia and, therefore, we present the first case of this lesion in our country. This tumor should be considered when performing the differential diagnosis of slow-growing lesions in the caruncle of elderly patients. The tumor is benign and complete resection is the definitive treatment.

References