Cameo

Mucin-poor follicular mycosis fungoides

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A 49-year-old woman was admitted with generalized pruritus which she had for the last 4 years. Three months ago she developed erythema on her face, alopecia totalis, an erythematous macular eruption with follicular hyperkeratoses on the trunk and limbs (Fig. 1). She had bilateral palpable axillary lymphadenopathy. Histologic examination of the biopsies taken from the erythematous areas on the trunk and scalp revealed a folliculocentric infiltration composed of atypical, small and medium-sized mononuclear cells, intermingled with reactive lymphocytes, histiocytes, plasmocytes, rare eosinophils, and giant cells without involvement of the epidermis (Fig. 2). The infiltrate surrounded and invaded the hair follicle epithelium without destroying it. With alcian blue staining, only small amounts of mucin were detected within the epithelium of the hair follicles. By the immunohistochemistry performed, folliculocentric infiltration was mainly composed of CD3(+), CD4(+), CD8(–) lymphocytes. A full blood count, peripheral smear, erythrocyte sedimentation rate (ESR), the concentration of nitrogen in the form of urea in the blood (BUN), creatinin, transaminases, serum electrolytes, C-reactive protein (CRP), IgE, serum lipids, serum lactate dehydrogenase, urinalysis, roentgenogram and CT scan of chest were normal. Beta 2 microglobulin was 3.15 mg/L (normal range 1.2–2.5 mg/L). In the biopsy of the axillary lymph node, there was a focal infiltration of atypical T-cells in the interfollicular area. She was given psoralen-UVA (PUVA) treatment for 6 months (85 sessions, in escalating doses with a total 71.8 j/cm^2) which resulted in a partial healing of the pruritus, erythematous plaques, follicular hyperkeratoses, and patchy hair regrowth. She then received oral methyl prednisolone, 40 mg daily for 3 weeks and the dose was gradually decreased and eventually reduced to 16 mg daily in 2 months. This resulted in healing of the pruritus, improvement in the erythematous plaques and follicular hyperkeratoses and axillary lymphadenopathy. Beta 2 microglobulin levels decreased to normal range (2.27 mg/L). After taking the 16 mg daily dose of the prednisolone for 6 months, her complaint of itching recurred. Erythematous plaques and follicular hyperkeratoses were noted again. The dosage of the steroids was increased to 40 mg daily and PUVA treatment was restarted. She is currently receiving oral methyl prednisolone and PUVA.

Discussion

Cutaneous T-cell lymphoma (CTCL) many have heterogeneous clinical and histological features. A rare form of CTCL, follicular mycosis fungoides (FMF), first described by Peroya *et al*. in 1997, is an entity differing from alopecia mucinosa/follicular mucinosis associated with mycosis fungoides with regard to its clinical presentation and histology. Follicular mycosis fungoides is a rare variant of cutaneous T-cell lymphoma, histologically characterized by infiltrates of atypical CD4+ lymphocytes around and within the epithelium of the hair follicles.[1–3] The recently described two main criteria for FMF were suggested as (a) pilotropism of the infiltrate without modification of the pilofollicular walls such as necrosis and spongiosis, and (b) the presence of a monomorphous lymphocytic infiltrate of hyperconvoluted helper T lymphocytes showing pilotropism.[3,4] This pilotropic T cell lymphoma can

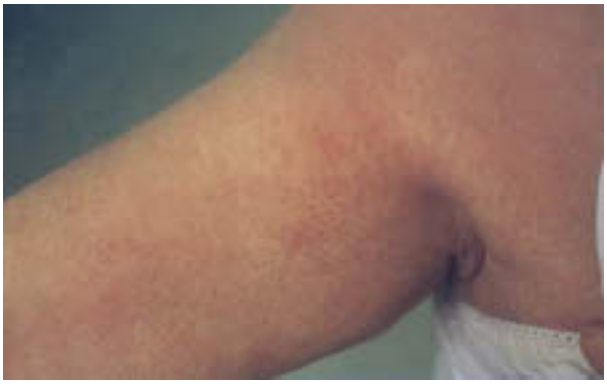

Figure 1 Follicular papules are seen on the upper extremities

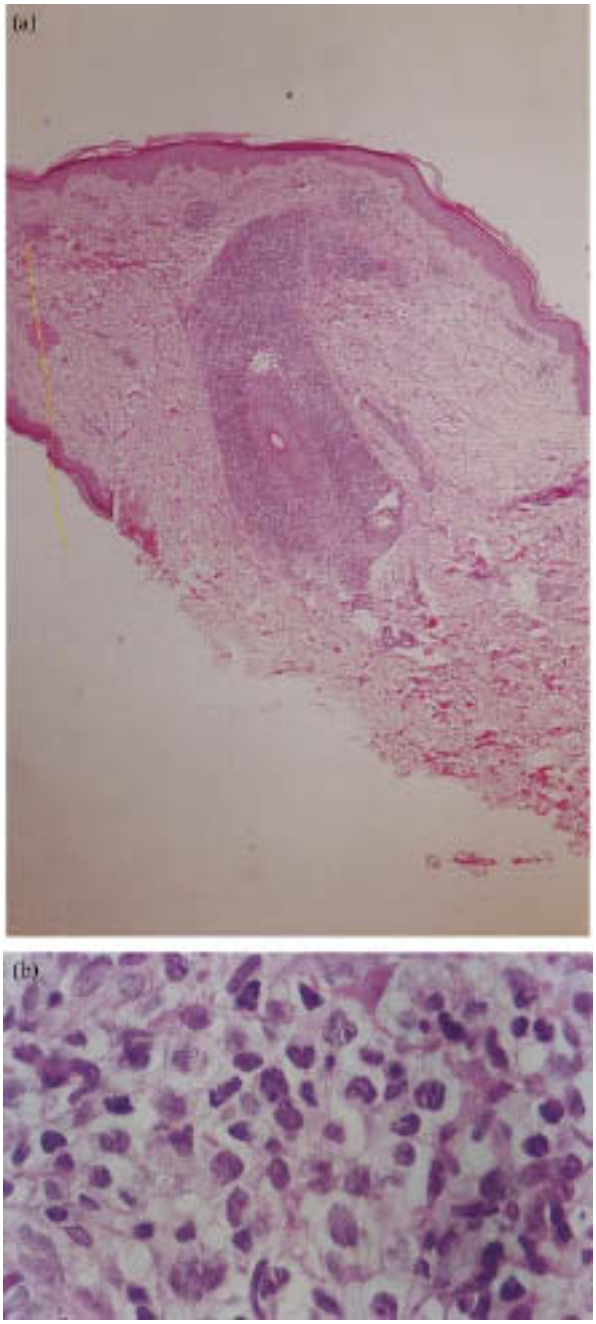

Figure 2 (A) FMF; a folliculocentric infiltration demonstrated in the dermis. (H & E × 200) (B) FMF; typical convoluted lymphocytes both surrounding and involving the follicular epithelium intermingled with histiocytes and eosinophils (H & E × 1000)

be distinguished from follicular mycosis (FM) associated with mycosis fungoides (MF), which is characterized by deposits of mucin in the follicular epithelium in addition to a polymorphous infiltrate composed of lymphocytes and eosinophils both superficial and deep perivascular and interstitial accentuated around the hair follicules.[5] Follicular mycosis fungoides typically does not display prominent mucin deposition but mucinosis associated with pilotropism has been reported to be extremely rare.[4,6] It is still debatable whether this mucin-poor FMF like our case can be reliably distinguished from FM associated with MF. However, the absence of prominent mucin deposition, as well as the presence of prominent folliculocentric infiltration in serial biopsies were considered as helpful clues for the diagnosis of FMF in our case.

The pathogenesis of prominent pilotropism in FMF is not clear, however, it has been found out that in FMF the expression of intracellular adhesion molecule-1 (ICAM-1) which plays a role in the interaction of lymphocytes and keratinocytes, was demonstrated in the follicular epithelium, whereas it was negative for epidermal keratinocytes. This molecule plays a role in the interaction of lymphocytes and keratinocytes.[1]

Clinically, the lesions of FMF were similar to classic MF, but also contained pilofollicular lesions such as follicular papules and keratosis, pseudocomedones, epidermal cysts and keratosis spinulosa and also areas of alopecia.[1–3] Other than follicular mucinosis associated with MF, follicular lymphomatoid papulosis should be included in the differential diagnosis. However, the lesions of follicular lymphomatoid papulosis tend to involute spontaneously leaving scarring.[7]

Various treatment modalities have been used for FMF, either as a single agent or in combination. These include topical steroids, PUVA, retinoids, nitrogen mustard, carmustine, mechlorethamine, interferon alpha, extracorporeal photopheresis and electron beam therapy[7–9]. The cystic lesions of FMF were often resistant or responded only partially and recurred on cessation of these treatments. Fraser-Andrews *et al.*[10] have used intermittent cyclophosphamide for their patient's cystic lesions and reported a response to treatment. We have used PUVA and then oral prednisolone and our patient responded partially.

In conclusion, the patient presented is a mucin-poor FMF with follicular papules accompained by plaques, and a histology showing folliculocentric infiltration. We suggest that the presence of small amounts of mucin may not rule out the diagnosis of FMF as demonsrated in the current case.

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Cameo

Erythema nodosum associated with sporotrichosis

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Case 1 A 34-year-old woman had ulcerated lesion 2 cm in diameter on the right leg of 2 months' evolution. She also presented painful erythematous nodules on lower limbs accompanied by arthralgia appearing 1 month after the initial lesion (Figure 1a). The patient reported having been scratched on the right leg by a cat with sporotrichosis 15 days before the initial symptoms. Examination of the ulcerated lesion showed growth of *Sporothrix schenckii*, and histological investigation of one nodule showed a mononuclear inflammatory infiltrate in the hypodermis with a predominantly septal distribution, negative upon culture for fungi (Figure 1b). Radiographic examination of left ankle showed increased soft tissue, while other ancillary tests were normal. The patient was treated with itraconazole 100 mg/day for 4 months, with regression of Erythema nodosum (EN) on day 20.

Case 2 A 25-year-old woman presented to our facility for evaluation of an ulcerated lesion measuring 3 cm on her left wrist accompanied of ascending subcutaneous nodules on her lower limbs. She reported having been scratched on the site of a subsequent lesion 10 days previously by a cat with sporotrichosis. Culture of ulcerated lesions produced *S. schenckii*. The patient was placed on itraconazole 100 mg/day. One week after initiating treatment, she suffered a second scratch, which was followed, 7 days later, by nodular lesions located on the lower limbs accompanied by arthralgia and fever. Histopathology showed a predominantly hypodermic perivascular mononuclear inflammatory infiltrate with a septal distribution, forming small granulomas and producing a negative culture (Figure 2b). Radiography of ankles showed increased soft tissue. The treatment was maintained, with regression of EN after 50 days and total regression of lesions by the third month.

Case 3 A 12-year-old boy was admitted,with an ulcerated 2 cm lesion on the left foot with slightly infiltrated borders and secretion, accompanied by painful groin adenomegaly. Physical examination also revealed a recent scar measuring 1.5 cm on the left knee. He denied trauma but reported household contact with 11 cats with sporotrichosis. Upon his return visit 40 days later, the patient presented painful erythematous nodules on his knees and thighs, plus knees

and ankles edema with arthralgia (Figure 3a). Culture of ulcerated lesion, by now nearly healed, showed *S. schenckii*. Histopathological examination of a nodule showed septal and lobular hypodermic infiltrate with formation of granulomas and negative fungal culture (Figure 3b). He was treated with itraconazole 100 mg/day for 3 months, with regression of EN and arthralgia on day 20 of treatment.

Discussion

Erythema nodosum (EN) is characterized by an acute eruption of erythematous nodules on the anterior aspect of the lower limbs, along with fever, arthralgia, and malaise. It is a clinical syndrome probably due to a hypersensitivity mechanism[1] whose main etiologies are infection, neoplasia, inflammatory disease, and use of medication.[2,3]

In fungal infections, EN has been described mainly with systemic mycoses such as histoplasmosis and coccidioidomicosis.[4,5] In these cases, EN appears to play a protective role, leading to a more benign evolution of the disease. Sporotrichosis as a cause of EN has not been reported previously in the literature. We present three cases of EN in patients with sporotrichosis from an epidemic involving humans, cats, and dogs in Rio de Janeiro, Brazil.[6] Sporotrichosis is an infection with a typically subacute or chronic evolution, affecting humans and animals and caused by the dimorphous fungus *S. schenckii*. It is rarely transmitted by animals.[7] In the cases presented here, infection occured due to scratches or household contact with diseased cats. *Sporothrix schenckii* was recently demonstrated in the claws of cats[8] but feline-to-feline transmission can occur even in the absence of trauma.[9]

In the household environment, daily exposure to the *S. schenckii* present in lesions which are usually rich in parasitic forms in the cat could lead to subclinical re-infection and hypersensitivity in the host, leading to the appearance of EN, not described previously in association with sporotrichosis. It is interesting to note that EN appeared in Case 2 after the second scratch by a cat with sporotrichosis.

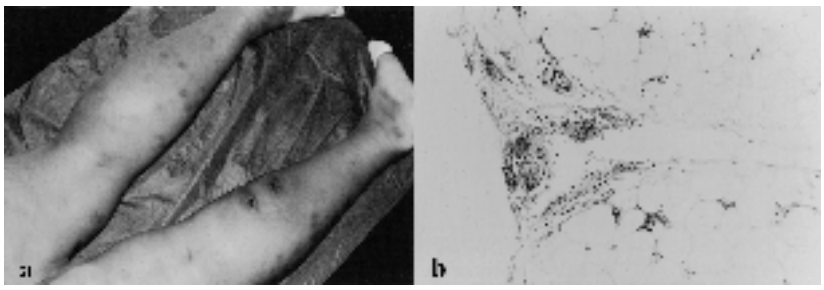

Figure 1 (a) Ulcerated lesions on right calf and erythematous nodules on lower limbs. (b) Histopathology of one lower limbs nodule, displaying small granuloma in the subcutaneous cellular tissue (HE, 4 ×)

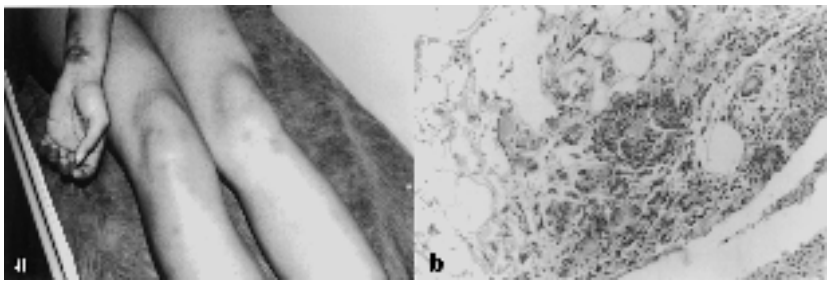

Figure 2 (a) Ulcerated lesion with infiltrated borders on left wrist and erythematous nodules on lower limbs. (b) Histopathology of one lower limbs nodule, showing granulomatous tissue reaction in hypodermis (HE, 20 ×)

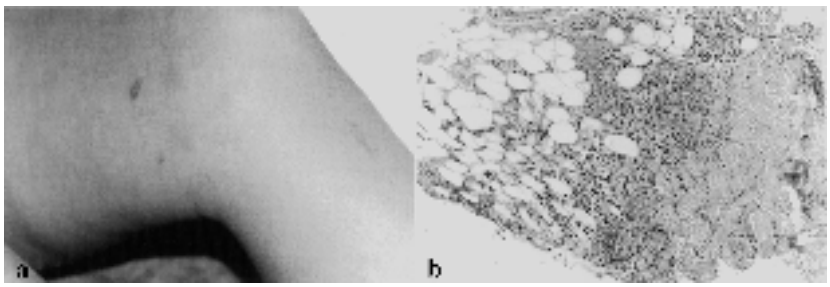

Figure 3 (a) Cicatricial lesion and erythematous nodules on left knee (b) with biopsy showing significant inflammatory infiltrate in dermis and hypodermis, with giant cells (HE, 20 ×)

Prospective studies are necessary to better determine whether the source of infection influences the expression of EN associated with sporotrichosis, and whether EN might play a protective role, as observed in certain systemic mycoses. In addition, since sporotrichosis can involve both subclinical cases and spontaneous cure, we suggest that should be included in the etiological investigation procedures of EN.

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Cameo

Sudden onset of melanuria in a patient with metastatic melanoma and toxic epidermal necrolysis

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Drug names
temozolomide: Temodar
dexamethasone: Decadron
phenytoin: Dilantin
acyclovir: Zovirax
vancomycin: Vancocin
methylprednisolone: Solu-Medrol
fluconazole: Diflucan

A 46-year-old man presented to our institution with blisters and eruption on the body and oral mucosa. He had a history of metastatic melanoma to the brain and had undergone radiation therapy to the head and chemotherapy with temozolomide. He was then started on dexamethasone and phenytoin. One month later, he developed a fever of 39.5 °C and an eruption in the axilla and groin. He was admitted to another hospital with a presumptive diagnosis of disseminated herpes zoster and was started on acyclovir, vancomycin, methylprednisolone, and fluconazole. The phenytoin was discontinued. Three days after admission, the eruption progressed and the patient developed respiratory distress. Biopsies from several lesions showed focal necrosis of keratinocytes with minimal superficial perivascular inflammation, consistent with toxic epidermal necrolysis. He was intubated and transferred to our medical center.

On physical examination, the patient had exfoliation of over 70% of his body surface area (Fig. 1), and scattered blisters were observed on the hands, chest, abdomen, and back. He also had crusted hemorrhagic plaques on the lips and conjunctiva. The patient was admitted with a diagnosis of toxic epidermal necrolysis, secondary to phenytoin.

At the time of admission, the patient was noted to have black urine (Fig. 2). His urine analysis showed moderate proteinuria, 8.0 mg/dL of urobilinogen (normal range, 0.2–1 mg/dL), coarse granular casts, amorphous phosphate crystals, and was nitrate positive. The blood urea nitrogen (BUN) and creatinine levels were within normal limits. A urine sample was sent to the laboratory for cytospin and cell block analysis. Melanin was present in macrophages as detected by Fontana–Masson stain (Fig. 3). A heme stain for iron was negative. The patient was

treated with supportive therapy and high-dose intravenous immunoglobulin (1 g/kg/day × 4). The patient's skin slowly improved over the 6-week hospital course with full re-epithelialization by the end of his hospital stay. Computed tomography (CT) scan of the head showed the presence of multiple hemorrhagic metastases involving the brain bilaterally, edema and compression of the left ventricle, and a midline shift, which was consistent with metastatic melanoma. CT scan of the abdomen and pelvis demonstrated a large low-density focus within the right lobe of the liver, also consistent with metastatic involvement. There was no evidence of metastatic disease in the kidneys or the urinary tract. Given the extent of his disease, he was discharged to a hospice facility.

This case is presented because melanuria is a rare complication of metastatic melanoma and, unlike this case, most cases of melanuria have been associated with diffuse melanosis and/or metastasis to the genitourinary tract.

Discussion

Melanin (brown–black pigment of eumelanin or yellow–red pigment of pheomelanin) can be elevated in the blood of patients with malignant melanoma.[1] Studies indicate that the measurement of melanin precursors and metabolites, such as 5-*S*-cysteinyldopa (a pheomelanin precursor), in blood and urine may be useful in the detection of early metastasis in patients with metastatic melanoma.[2,3]

Melanuria, however, is a rare finding in patients with malignant melanoma. It is usually seen in patients with diffuse melanosis and primary or metastatic melanoma to the genitourinary tract.[4–8] Diffuse melanosis is clinically described as a gray–blue discoloration of the skin and mucous membranes. This blue color is due to the aggregation of melanin-containing dermal macrophages in the perivascular spaces.[8–10] The tumor-derived melanin granules circulate in the systemic blood and are phagocytosed by endothelial cells and macrophages before being excreted in the urine.[8] The specific cytologic findings in the urinary sediment in diffuse melanosis are pigment-laden cells and brown casts with no evidence of malignant cells.[11] In the case of diffuse melanosis, computed tomography (CT) scan and other imaging studies should be performed to rule out metastasis to the genitourinary tract and other organs. Metastasis to the urinary tract, with the most common site being the kidneys, is the other cause of

Figure 2 Patient's urine (melanuria) at the time of admission

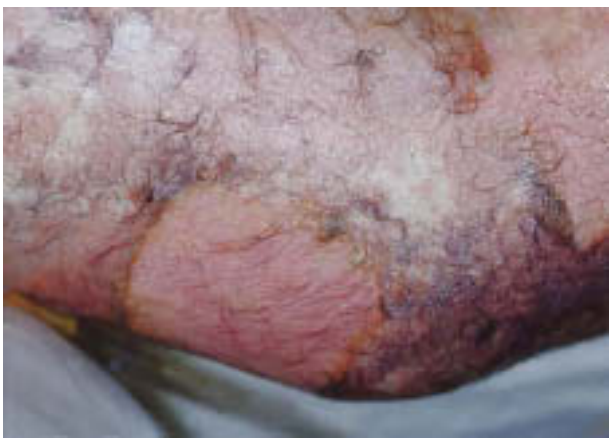

Figure 1 Extensive desquamation over the patient's flank and thigh

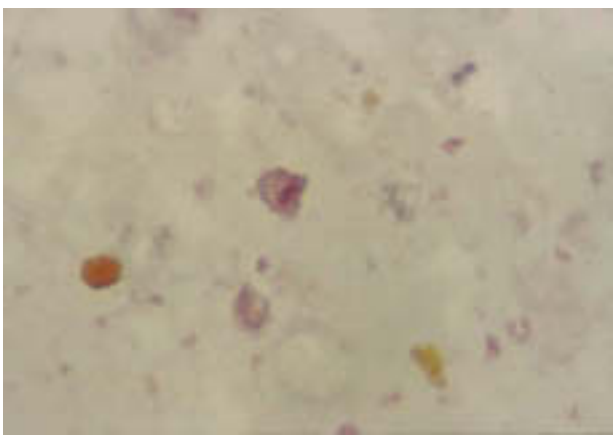

Figure 3 Urine cytospin showing melanin within macrophages

melanuria.[12] The detection of melanoma involving the genitourinary tract is usually discovered at autopsy.[7,13] Cytologic examination of the urine in these cases has been reported to be a very useful method for the detection of metastasis to the genitourinary tract, even before the primary melanoma is diagnosed.[7,13,14]

Melanoma cells in the urine are large, oval-shaped, and solitary with regularly contoured, eccentric nuclei and centrally placed macronucleoli.[14] Granular brown–black melanin pigments are present in a thick cyanophilic cytoplasm.[7,13] Similar cells, however, can also be seen in transitional cell carcinoma, renal adenocarcinoma, metastatic cancers, and cells infected with cytomegalovirus.[14] Histochemical characterization of melanin is therefore essential.[14] CT scan usually shows renal involvement.

Piva and Koss[7] reported a case in which a urine sample was positive for melanin, while the autopsy showed no involvement of the urinary tract; however, the kidneys were dark in color and there were melanin casts in the renal tubules. It appeared that the melanin pigments were excreted from tubular epithelial cells containing melanin. Therefore, they discussed the importance of the malignant nuclear features before making the correct diagnosis.

Our patient had no evidence of diffuse melanosis or metastasis to the genitourinary tract, as shown by CT scan. Furthermore, although melanin pigments were present in the urine, no malignant cells were observed and the patient's melanuria resolved following intravenous hydration. Our hypothesis is that a combination of factors contributed to this patient's melanuria. Necrosis of the skin following toxic epidermal necrolysis and/or radiation to the brain probably produced damage to a large number of melanocytes, leading to a high concentration of melanin in the systemic circulation and therefore excretion into the renal tubules and urine. In addition, the patient's probable prerenal azotemia, which commonly occurs in toxic epidermal necrolysis, could have caused tubular damage, leading to damage and inflammation of the renal tubules and migration of melanin-containing macrophages to the kidneys and subsequently to the urine.

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