To the Editor:

We present the case of a 31-year-old woman with no relevant medical history, who consulted because of lesions on the backs of the hands related to minor traumas; the lesions worsened in the summer leaving residual hyperpigmentation (Figure). The patient had phototype III skin and displayed discrete hypertrichosis in the zygomatic areas. Photosensitive dermatosis was suspected and a battery of tests was requested to measure liver function, serum iron, transferrin and ferritin levels, blood and urine porphyrins, and photosensitivity.

High levels of porphyrins were found in the 24-hour urine collection: 2104 µg/L (normal values: <200 µg/L), 85% of which were uroporphyrins. Levels of porphyrins in the plasma were 25 µg/L, exceeding the normal range (<10 µg/L). Levels for serum iron were 2104 µg/L (normal values: 92-155 µg/dL); transferrin: 310 mg/dL (normal values: 205-365 mg/dL); and ferritin: 175 µg/mL (normal values: 13-160 µg/mL); all of which were high or at the upper limit of the accepted normal range. Liver ultrasound showed no abnormalities.

A diagnosis of porphyria cutanea tarda (PCT) was reached on the basis of the symptoms, clinical indicators, and test results. The patient reported no family history of skin lesions or liver disease. Oral contraceptives (OC) taken by the patient for 6 months prior to consultation were initially considered a possible trigger for the PCT, but the lesions continued to appear after this medication was suspended. There were no other apparent triggers as the patient was not a habitual drinker and tests for hepatitis were negative.

Genetic studies for the most common hemochromatosis mutations (C282Y, H63D) showed the patient to be heterozygous for C282Y. This could explain the discreet abnormalities seen in the iron metabolism and, in conjunction with the use of OC, could have contributed to her developing PCT. In view of the patient’s wish to start a family, her husband was tested for hemochromatosis. He was found to be heterozygous for the H63D mutation.

Treatment consisted of phlebotomies at 2 week intervals and this led to remission of the skin lesions and a return to normal porphysrin levels in both plasma and urine.

We were unable to determine the enzymatic activity of erythrocyte uroporphyrinogen decarboxylase (URO-D) as follow-up of the patient was incomplete.

PCT is the outcome of a deficit in or inactivation of the URO-D enzyme, resulting in the accumulation of photosensitive metabolites that are excreted in the urine and feces.1

There are three main types of PCT: I, II, and III.2 Type I—the sporadic variety—is most common, with inactivation limited exclusively to the liver in patients with no previous family history. Type 2—the familial variant—is characterized by the inactivation or deficiency of the URO-D enzyme in all tissues. Type III is characterized by inactivation in the liver where there has been some previous family history of the condition.

Onset tends to occur in adulthood, and there are several known triggers: viral hepatitis, alcohol, OC and hormone replacement therapy, polychlorinated hydrocarbons, hemodialysis, and situations leading to iron overload like hemochromatosis.3,4 The most common trigger varies according to age, sex, and geographical location. In men, alcohol abuse and chronic viral hepatitis are the most common triggers, while in women, hormone therapy is the single factor implicated in a large percentage of cases. Exposure to hydrocarbons has been identified as a trigger in developing nations, while infection by the hepatitis C virus is a more common element in the Mediterranean and Latin American countries.2

Hemochromatosis is a autosomal recessive genetic condition with a prevalence of 1/200.5 It is characterized by increased intestinal absorption of iron that...
accumulates in the tissue (liver, pancreas, myocardium, skin, joints), where it produces clinical symptoms. Hemochromatosis is suspected in premenopausal women where there is transferrin saturation of more than 50% or ferritin levels of above 200 µg/L. Even though 80% of patients with PCT have hepatic siderosis and 60% have hyperferremia, less than 20% fulfill the criteria of hemochromatosis.

Various mutations associated with this disease have been identified recently. The most common of these—C282Y and H63D—are found on the HFE gene on the short arm of chromosome 6. In the former, tyrosine is replaced by cysteine at amino acid 282, while in the latter, histidine replaces aspartic acid at position 63. Eighty percent of these patients are homozygous for C282Y, and 20% are double heterozygous for both this and H63D.

The prevalence of these mutations varies from one population to another. The former is predominant in Nordic and central European countries and among the Celtic populations of Spain (Galicia and Asturias), while the second is common in the Mediterranean area. In Spain, there is 1.7% prevalence of C282Y, and 20% are double heterozygous for both this and H63D.

The subtype of PCT could not be reliably established for this patient as the erythrocyte URO-D and URO-D genetic tests were not undertaken. As a result, even though there was no previous family history of photodermatosis or liver disease, type II PCT could not be entirely ruled out. Although this matter has little bearing on treatment options in such cases, the information would prove useful as a basis for providing genetic counseling, above all for young women experiencing PCT in the absence of other triggers.

### Table. Studies Including a Series of Healthy Patients With Porphyria Cutanea Tarda (PCT) in Which the C282Y and H63D Mutations Were Observed to be More Common in Patients Affected by PCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Mutation</th>
<th>PCT</th>
<th>Controls</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberts (1997)</td>
<td>C282Y</td>
<td>44%</td>
<td>11%</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Santos (1997)</td>
<td>H63D</td>
<td>23%</td>
<td>4%</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>Sanpietro (1998)</td>
<td>H63D</td>
<td>29%</td>
<td>13%</td>
<td>Italy</td>
</tr>
<tr>
<td>Martinelli (2000)</td>
<td>C282Y</td>
<td>17%</td>
<td>4%</td>
<td>Brazil</td>
</tr>
<tr>
<td>Bulaj (2000)</td>
<td>C282Y</td>
<td>34%</td>
<td>13%</td>
<td>USA</td>
</tr>
<tr>
<td></td>
<td>H63D</td>
<td>22%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Chiaverini (2003)</td>
<td>C282Y</td>
<td>18%</td>
<td>1%</td>
<td>France</td>
</tr>
<tr>
<td></td>
<td>H63D</td>
<td>54%</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>Frank (2006)</td>
<td>C282Y</td>
<td>15%</td>
<td>5%</td>
<td>Germany</td>
</tr>
<tr>
<td></td>
<td>H63D</td>
<td>35%</td>
<td>29%</td>
<td></td>
</tr>
</tbody>
</table>

These mutations appear to be more common in patients with PCT due to the fact that homozygotes, heterozygotes, and double heterozygotes for these mutations are more likely to produce iron overload, which acts as a trigger for PCT, either alone or concomitantly. The H63D mutation in heterozygosis is not significant in iron overload and the development of PCT, but its role increases in double heterozygosis.

Several studies with a series of patients have demonstrated the previous association. Thus, in most of Europe, including Spain, the United States, and South America, C282Y is the most common mutation, while in Italy, mutation H63D is more widespread (Table).

The treatment of choice for PCT is phlebotomies at 2 week intervals, extracting 200-500 mL according to tolerance. Clinical response is seen within 2 to 3 months and tests prove normal at 12 months. Serum iron levels of less than 25 µg/L are sufficient to control the disease. Other accepted treatment options include the antimalarial drugs chloroquine and hydroxychloroquine, which help achieve faster results when combined with bleeding.

There is a poorer response to antimalarials in those cases of significant iron overload that tend to occur in patients homozygous for C282Y, and it may therefore be necessary to combine the 2 options.

Trigger factors like hormone therapy, alcohol, liver failure, and viral hepatitis must be corrected or minimized.

This article aims to call attention to the fact that genetic screening for hemochromatosis can be useful in patients with PCT in whom no clear trigger can be identified, as this test is readily available within the Spanish health system and can help to diagnose these latent hemochromatoses. Also, as these are relatively common mutations (up to 20% of the population may be carriers) genetic testing and counseling could be provided for couples where one member is known to have PCT and some of the mutations described above.

In this case, both members of the couple were carriers of the most common mutations for hemochromatosis. This situation gives them a 25% chance of heterozygous descent, although penetrance of this disease is known to be low and therefore the possibility of their children suffering hemochromatosis will be lower.
Melanoma in a Patient With Parkinson Disease

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To the Editor:
There has been discussion of the link between melanoma and Parkinson disease (PD) in the literature, along with the possible causal relationship between levodopa and rasagiline therapy and the appearance of melanoma. We present the case of an 81-year-old woman, Caucasian, phototype III, home maker, with no history of sunburn or family history of melanoma, who consulted for a pigmented lesion on the right cheek that had appeared a year earlier. The patient had a personal medical history of idiopathic PD treated with Sinemet (levodopa/carbidopa) and Azilect (rasagiline) for the last 18 months. We reviewed the literature in order to

The Sinemet prescribing information sheet warns of the possibility of levodopa activating melanoma, thereby contraindicating its use in patients with suspect skin lesions or a history of melanoma. The association between treatment with levodopa and melanoma was first described in 1972 by Skibba et al., who published a case of the recurrence of melanoma following treatment with levodopa. The hypothesis stems from the fact that dopamine (the deficient neurotransmitter in PD) and melanin share common metabolic pathways and it is suggested that exogenous levodopa could have some effect on melanin synthesis, increasing melanogenesis and stimulating melanoma growth. Individual cases and series of cases along the same lines were published from the 1970s to the 1990s. In 2003, Fiala et al.1 published a review of all 43 cases published to date, adding a further 11 cases from their own institution in Texas, United States. They analyzed the average age at diagnosis of the 2 diseases; whether the diagnosis of melanoma occurred before or after initiating treatment with levodopa; the average time between starting treatment with levodopa and the appearance of the melanoma; and the average amount of levodopa consumed before the diagnosis of melanoma was made. The resulting data were heterogeneous and inconclusive on all fronts, whereby it was suggested that the relationship between treatment with levodopa and melanoma was more of a coincidence than a causal relationship.

In 2006, Olsen et al.3 in Denmark, published a retrospective case-control study (cases: 8090 patients with PD; controls: 32 236 people from the central register) in which they measured the prevalence of cancer from 1943 until the date of diagnosis with PD (using the same date in the corresponding controls). They found a greater prevalence of melanoma in patients with PD (odds ratio [OR] 1.44; confidence interval [CI], 1.03-2.01); this prevalence increased in the year prior to diagnosis with PD (OR 3.2; CI, 1.26-8.1). These data led them to the conclusion that there must be a common environmental or genetic factor in both diseases and that the association between the 2 is not due to treatment with levodopa. In 2007, the same authors published a retrospective study of a cohort of 14 088 patients with PD in which they measured the incidence of cancer from diagnosis with PD to 2002.4 They found an increased risk of melanoma compared with the general population (relative risk 1.85; CI, 1.37-2.46). There was a special link with melanoma in the idiopathic Parkinson group (OR 3.9; CI, 1.6-9.8), while this association was not statistically significant in the group of other forms of PD. Meanwhile, they confirmed that the risk of melanoma was not dependent on treatment with levodopa or on cumulative dose. They therefore concluded that the increased incidence of melanoma in patients with PD is restricted to those with idiopathic PD and that this is not treatment dependent.

In the case of rasagiline, the prescribing information sheet of Azilect (authorized in 2005) warns of a possible link with the appearance of melanoma, meaning that any suspicious lesion should be assessed by a specialist. The warnings on the prescribing information sheet were based on the findings of a randomized and placebo controlled clinical trial5 with 472 patients, in which 3 new cases of melanoma appeared (all in the treatment group). The results of a post-marketing study is currently pending.

In summary, there are no epidemiological studies that show a causal link between levodopa and melanoma, so this drug should not be withdrawn from patients with melanoma nor should its use be contraindicated in patients with a history of melanoma. We suggest modifying the prescribing information sheet to avoid anxiety in Parkinson patients who could also be affected by melanoma. At present there is a perceived link between PD and melanoma (see Zanetti et al.6) although this has not yet been ascribed to a common genetic cause or the presence of an external factor associated with both entities. As for the use of rasagiline, further studies are needed before a position can be taken on the matter.

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Conflict of Interests
The authors declare no conflicts of interest.

References
To the Editor:

There are several types of dermatosis that may occur around the melanocytic nevi, although there are few reported cases of each of these. The most representative of these dermatoses is halo nevus (Sutton nevus, leucoderma acquisitum centrifugum), but there are other named examples including Meyerson nevus (halo dermatitis), targetoid nevus, and a form of exudative erythema multiforme around the nevi (nevocentric EEM).

The most common nevocentric dermatosis is Sutton nevus or halo nevus, recognized by the presence of a colorless halo around the nevus that has been related to an immunological process caused by the nevus itself. In 1971, Meyerson described some patients with scaly erythema around the nevi—confirmed by histology to be a spongiosic dermatitis—that resolved spontaneously. Targetoid halo nevus is another condition reported around melanocytic nevi—this is believed to be an immune phenomenon caused by halo nevus that resolves following removal of the nevus. There is also one case of nevocentric psoriasis described by Shifer et al in 1992. There are very few cases of nevocentric EEM reported in the literature, and, unlike the case of our patient, none of them occurred during pregnancy. Humphreys and Cox described one case of unknown etiology in 1988 in a patient treated with thiabendazole, but no later case has been related to any other drug. All the cases described have been related to a history of labial herpes, as was the case in our patient. In all the cases described, histology confirmed the presence of a lymphocytic infiltrate in the dermis around the nevi cells, along with keratinocytic degeneration and necrosis in the epidermis, suggestive of nevocentric EEM. The progression of this disease is identical to that seen in non-nevocentric EEM, which resolve spontaneously or following treatment with corticosteroids. Some authors use antiviral agents to accelerate healing in herpes, an option we did not consider for our patient.

We present the case of a woman in the fifth month of gestation, with no relevant history except for recurrent labial herpes, who consulted because of redness around several nevi. This initially consisted of halos of erythematous infiltrates covering an area 0.2 cm in diameter around the nevi; as time progressed these changed into concentric targetoid halos around most of the nevi on the body and face (Figures 1 and 2), with some isolated targetoid lesions in areas where there was no nevus. The patient reported lesions on the upper lip compatible with labial herpes in remission. Clinical and histological study enabled diagnosis of nevocentric EEM. Prednisone 30 mg/d was prescribed and the lesions disappeared within 5 days.

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Reference


Symmetrical Peripheral Gangrene and Disseminated Intravascular Coagulation Associated With Pneumococcal Sepsis

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To the Editor:

Symmetrical peripheral gangrene (SPG) is a rare but devastating complication of septicemia. Most cases of SPG are associated with disseminated intravascular coagulation (DIC).

We present the case of a 35-year-old woman who had undergone splenectomy due to abdominal trauma at 3 years of age; she was referred to hospital with fever and severe prostration with onset 6 days previously in the form of fever, myalgia, and dry cough. Tachycardia, tachypnea, hypotension, and fever were all evident in the initial evaluation. Closer physical examination revealed nothing except for the presence of bibasal crackles during the cardiopulmonary auscultation. Initial complementary tests clearly showed the presence of leukocytosis with left shift (leukocytes: 11 600/µL [range: 4000-10 000/µL], neutrophils: 91% [40%-75%], band forms: 46% [1%-3%]), mixed acidosis, sinus tachycardia, and bilateral pleural effusion with an air bronchogram in the retrocardiac area. Serum biochemistry, coagulation study, biochemistry, and urine sediment, as well as cerebrospinal fluid (CSF) analysis were normal. Due to her hemodynamic state and the initial diagnosis of sepsis caused by encapsulated bacterial respiratory infection, the patient was transferred to the intensive care unit (ICU), where she was stabilized with a volume infusion and perfusion of vasoactive amines and empirical treatment with cefotaxime 2 g every 6 hours and intravenous azithromycin 500 mg/d.

Six hours after admission to the ICU the patient was re-evaluated clinically and petechial skin lesions were found on the acral zones of the extremities, coalescing to form ecchymotic plaques. Peripheral pulses were palpable. A second complete blood count and coagulation study performed at this time were consistent with DIC (platelets: 20 000/µL [150 000-400 000/µL], prothrombin time: 20 s [10-12.5 s], partial thromboplastin time: 82.5 s [20-40 s], fibrin degradation products: 650 µg/mL [< 8 µg/mL], D-dimer: 8947 ng/mL [< 500 ng/mL]). Red cell concentrates and platelets, as well as fresh plasma, were administered. The patient’s urine tested positive for Streptococcus pneumoniae antigen and the same agent was isolated in the CSF culture. Antibiotic susceptibility testing revealed the organism was sensitive to penicillin and treatment was initiated with doses of 4 million units every 6 hours. The patient progressed well clinically over the following days, with the skin lesions healing except on several fingers on both hands where necrosis and dry gangrene with mummification occurred (Figure). When the necrotic areas had been outlined, 15 weeks later, these areas were amputated and reconstruction was completed with flaps.

SPG is an uncommon but well documented syndrome first described by Hutchinson in 1891. It consists of symmetrical gangrene in acral regions with no evidence of large-vessel occlusion or vasculitis. The lesions begin in the form of erythema or purpurp lesions that develop...
into gangrene within 24-48 hours. Hemorrhagic blisters are common as are proximal purpural zones that do not always develop into necrosis.2 SPG has been linked to many underlying medical processes, and is most prevalent in serious infections in patients with certain risk factors.2-4 The most commonly implicated microorganisms are meningococci, pneumococci, streptococci, and staphylococci.2 SPG associated with pneumococcal sepsis principally affects splenectomized patients and is considered to be an extremely serious condition with high rates of associated morbidity and mortality.3,5 Up to 85% of cases of SPG are linked to DIC.1-5 Although it has been proposed that DIC leads to ischemia and posterior gangrene of the acral zones1 through the formation of intravascular clots in the microcirculation, other authors have related SPG to an initial spastic rather than thrombotic process in the vessels.3 Other factors potentially present in septic patients (severe hypotension, endothelial damage, microembolism, and the use of inotropic drugs) could also play a role in the pathophysiology of this entity.6,7 There is no specific treatment for SPG. Treatment of the underlying cause and DIC is of vital importance. Isolated cases of SPG have been successfully treated through sympathetic blockade,1 leukopheresis and plasmapheresis,8 acetylsalicylic acid,9 or a combination of anticoagulants and vasodilators.10 Early amputation is contraindicated, as secondary infection of the necrotic tissue is uncommon and delimitation of the ischemic lesions occurs with time. Initially, treatment is based on protection of the extremities and nursing care, with debridement, skin grafts, and partial or total amputation performed later.11 Surgery must be followed by rehabilitation of the patient with physiotherapy in order to conserve the highest possible level of functionality.

We wish to use this case to stress that, in the clinical setting of sepsis, SPG is considered a valuable skin marker of DIC and can therefore be seen as a sign of a very poor prognosis in this group of patients.

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Conflicts of Interest
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References
Toxic Dermatitis Due to Capecitabine: Presentation of 2 Cases and Literature Review

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To the Editor:

Capecitabine is a chemotherapeutic agent of the fluoropyrimidine family, indicated in metastatic colorectal cancer and advanced breast cancer. Its main cutaneous adverse effect is hand-foot syndrome (HFS); cases of skin hyperpigmentation, nail changes, and alterations of the mucosas secondary to this drug have also been reported. Capecitabine is converted to 5-fluorouracil by the enzyme thymidine phosphorylase, which is found in its highest concentration in tumor tissue. The drug is administered orally and its systemic adverse effects are less severe than those of 5-fluorouracil. We present 2 new cases of toxic dermatitis due to capecitabine where, in addition to HFS, there were localized skin hyperpigmentation and marked nail changes.

The patients were 2 men of 53 and 79 years of age, diagnosed with Duke stage III adenocarcinoma of the colon. After laparoscopic sigmoidectomy, they started adjuvant treatment with capecitabine (Xeloda), the first at a dose of 4000 mg/d and the other at 3000 mg/d. The first patient was seen after the third cycle of chemotherapy, with a 15-day history of skin lesions affecting the palms of the hands, with no associated palmar-plantar dysesthesia. On physical examination, we observed brownish macules of 0.3 cm diameter on both palms, associated with marked desquamation, periungual hyperpigmentation, and moderate erythema of the distal phalanges (Figure 1).

The second patient reported palmar-plantar erythema and erosions that started after the second cycle of capecitabine. Examination revealed intense palmar-plantar erythrosis and periungal desquamation. In addition, we observed onychomadesis, subungual hemorrhages, and erosive periungal vesicular lesions (Figure 2). On histological examination, we observed no involvement of the epidermis. Mild dilatation of the superficial vascular plexus and pigment incontinence (hematoxylin-eosin, ×100) (Figure 3).
associated with erosive periungual vesicular lesions and marked nail changes (Figure 2). The diagnosis of toxic dermatitis due to capecitabine with associated HFS was confirmed by skin biopsy (Figure 3). Treatment was started with topical corticosteroids and antibiotics; in the first case the dose of capecitabine was reduced to 2500 mg/d and the medication was discontinued in the second. The patients presented a progressive clearing of the skin lesions, with persistence only of mild paronychia and secondary onychodystrophy 4 months later in the second patient.

HFS secondary to capecitabine occurs in 50% to 68% of patients treated with this drug.² It is characterized by palmar-plantar erythema and pain and can lead to the appearance of distal ulcers if the dose of the drug is not reduced or the medication discontinued.³ The pathogenesis is unknown, although 2 theories have been proposed, both of which involve high local concentrations. The first hypothesis is based on the lower concentration of thymidine phosphorylase in the acral tissues, leading to a greater accumulation of the drug at that site. The second hypothesis suggests a greater elimination of the drug through the eccrine glands; as these glands are more concentrated in the palmar and plantar regions, there will also be a greater cumulative dose in these areas.² HFS can occur after the administration of other chemotherapeutic agents, mainly those of the fluoropyrimidine family, such as 5-fluorouracil, the active metabolite of capecitabine.⁴ The 2 patients presented here developed HFS of different severities, mild in the first case and severe in the second. Treatment is symptomatic with emollients and topical corticosteroids; the possibility of combining the chemotherapy treatment with a dihydropyrimidine dehydrogenase inhibitor has recently been proposed, as it appears to reduce the intensity of HFS. Dihydropyrimidine dehydrogenase is responsible for the catabolism of more than 80% of the fluoropyrimidines. If the addition of an inhibitor of this enzyme to chemotherapy treatment reduces the intensity of HFS, it would indicate that a degradation product of the drug is possibly responsible for the HFS.⁵

Other, less common cutaneous adverse effects of capecitabine include mucositis,⁶ onycholysis and onychomadesis,⁷ localized or generalized skin hyperpigmentation,⁸ acral sclerodermiform changes, and acquired palmar-plantar keratoderma.

Hyperpigmentation, which was marked in our first patient, occurs in 3% of patients treated with capecitabine.⁸ The first case was published in 2002,⁹ and the majority of cases have been reported in blacks and Asians; to date, we have only found 2 cases published in white individuals.⁸,¹⁰ No histological study was available in either of those cases, and we were therefore unable to perform comparative studies with the findings in our patient. The causes of hyperpigmentation are unknown, although 2 theories have been proposed: direct stimulation of melanogenesis, and postinflammatory hyperpigmentation.⁸ The fact that histological study in our patient showed pigment incontinence with no increase in the number of melanocytes would support the second hypothesis.

Nail changes caused by the use of capecitabine have hardly been mentioned in the literature. Our search produced only 1 published case; the proposed mechanisms of onycholysis were direct pharmacological toxicity or secondary bacterial or fungal colonization and, in the case of onychomadesis, absent mitotic activity of the nail matrix.

We present 2 new cases of toxic dermatitis due to capecitabine. In addition to the most common skin manifestation, HFS, there were other, very rare cutaneous toxic effects, including localized skin hyperpigmentation and nail involvement. As the use of this chemotherapeutic agent has been increasing recently, we must know of its possible adverse effects in order to improve clinical management.

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Conflicts of Interest
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References
Atypical Skin Metastases of Mucinous Adenocarcinoma of the Prostate With Signet Ring Cells

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To the Editor:

Skin metastases from carcinoma of the prostate are extremely rare. When they occur, they usually appear as multiple nodules in the suprapubic area or on the anterior aspect of the thighs. The appearance of distant lesions, outside the typical areas, is uncommon, with only 14 reports in the past 25 years. We report a case with an atypical presentation of skin metastases from adenocarcinoma of the prostate, also highlighting the utility of prostate specific antigen (PSA) as an immunohistochemical marker in skin metastases of unknown origin in elderly men.

The patient was a 62-year-old man who developed multiple nodular lesions on the thorax, axillas, and face; the lesions had developed over the previous 3 months. They were particularly numerous on the face, especially on the right side, extending towards the scalp (Figure 1). Associated symptoms included a 4-month history of dyspnea on exertion and costal pain on deep inspiration, together with difficulty urinating over the past 2 years. With a clinical suspicion of skin metastases, biopsy was performed of 1 of the lesions on the thorax. Histological study revealed a well-defined, dermal tumor nodule that did not reach the epidermis. It was formed of undifferentiated epithelioid cells, arranged in cords, and with signet ring morphology (Figures 2A and 2B). These cells were surrounded by a mucinous stroma (Figure 2C). Immunohistochemical analysis was intensely positive for cellular adhesion molecule 5.2 and PSA (Figure 2D). In view of the results obtained up to that time, additional tests were performed that focused particularly on the prostate; these tests had the following main findings: normocytic anemia, PSA of 3901 ng/mL, bilateral basal interstitial-alveolar infiltrates on the chest x-ray, and a thoracoabdominopelvic computed tomography showing thickened, irregular walls of the bladder; right paratracheal, subcarinal, para-aortic, and interaortocaval lymph nodes; and blastic bone changes, compatible with a metastatic pattern. On rectal examination, the prostate was found to be increased in size with no sulcus; it was poorly defined, fixed, and had palpable, stony-hard nodules in both lobes. Prostatic biopsy revealed adenocarcinoma affecting 90% of each lobe (Gleason score, 8). It was particularly noticeable that the histology of the primary tumor was similar to that of the skin metastases, with signet ring cells surrounded by a mucinous stroma. In view of the advanced stage of the disease, it was decided to administer palliative treatment with the gonadotropin releasing hormone analogue, goserelin, 10.8 mg subcutaneously every 3 months. The patient presented a progressive reduction in the number of skin lesions over the following months.

Skin metastases from internal tumors are uncommon in clinical practice. In women, the most common origin of skin metastases is adenocarcinoma of the breast, whilst...
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in men. The appearance of skin metastases in patients with cancer of the prostate is extremely rare: they represent only 1% of all skin metastases. The largest series of patients with skin metastases came from a study by Lookingbill et al., with a total of 4020 patients. In that series, despite the high frequency of carcinoma of the prostate, it was notable that there were no cases of skin metastases of prostatic origin. Current information about skin metastases from cancer of the prostate comes from the publication of small series or case reports; there are approximately 91 publications.

Based on those publications, we know that the typical clinical presentation is as multiple nodules in the suprapubic region and on the anterior aspect of the thighs or abdomen. Metastases outside these typical areas are very rare, with only 16 cases reported in the past 25 years (Table). When they appear, they are a sign of poor prognosis, indicating dissemination of the tumor. It is therefore common to find involvement of other body areas, particularly the pelvic bones and lymph nodes, in the study of tumor extension.

Exceptionally, skin metastases can be the first sign of prostatic disease. In these cases, it is essential to perform a detailed clinical study to look for associated systemic symptoms, as it is otherwise difficult to orientate the diagnosis towards skin metastases, and, more so, towards a prostatic origin. We draw particular attention to the utility of measuring the serum PSA in cases of suspected skin metastases.

From a dermatopathological point of view, metastases from carcinoma of the prostate are identified as nodules or sheets of tumor cells arranged between the dermal collagen fibers, showing glandular differentiation. Cells with a round nucleus and 1 or more eosinophilic nucleoli are typically observed on cytology. In our case, both the primary tumor and the metastases were of a mucinous adenocarcinoma with signet ring cells. This histological type of adenocarcinoma of the prostate is rare, but it is usually one of the most aggressive. The finding of signet ring cells in a mucinous stroma means that a primary tumor of the lung, stomach, or colon must be excluded; it is in these cases that the PSA becomes particularly important.
as an immunohistochemical marker, being an unequivocal sign of the prostatic origin of the skin tumors.

In summary, we present a case of atypical skin metastases of prostatic origin. We would like to highlight the atypical characteristics of this case—it developed in a relatively young individual for this type of tumor, the presentation was with multiple nodules at an uncommon site, the histological subtype was of signet ring cells in a mucinous stroma, and it was a highly aggressive—and the utility of PSA as an immunohistochemical marker in these cases.

**References**


Morphea Distributed Along Narrow Blaschko Lines

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To the Editor:

A 4-year-old girl, with no personal or family history of interest, presented pigmented lesions on the arms and trunk that had appeared approximately 1 year earlier. The initial lesions were papules of normal skin color that progressed to hyperpigmented, slightly raised lesions with a smooth, shiny surface and that were indurated and sclerotic. On examination, the lesions were observed along the length of the left upper limb, following 2 narrow lines from the wrist to the shoulder (Figure 1); this line continued across the left shoulder to the midline of the back. Another similar, linear lesion was found on the left side of the abdomen, following an S-shaped path.

There were no associated cutaneous or systemic symptoms. The complete blood count and biochemistry were normal. Antinuclear antibodies were positive at a titer of 1/160 and the results for perinuclear antineutrophil cytoplasmic antibodies, cytoplasmic antineutrophil cytoplasmic antibodies, and anti-Ro, anti-La, anti-Smith, anti-ribonucleoprotein, anti-Scleroderma DNA Topoisomerase I, and anti-Jo1 antibodies were negative. Histopathological examination revealed a normal epidermis with thickening of the dermis due to the presence of wide, sclerotic bands of collagen, mainly in the middle and deep dermis. In addition, there was a moderate inflammatory infiltrate formed of lymphocytes and a few plasma cells, with a superficial, deep, and perivascular distribution (Figure 2). The skin adnexa appeared atrophic, with no peripheral adipose tissue, and staining with orcein demonstrated preservation of the elastic fibers.

The lesions had been stable since their onset and it was therefore decided to maintain the patient under observation with no treatment.

Linear morphea is a rare disorder that usually occurs in childhood and can affect any area of the body surface. It includes what are considered to be special forms, such as morphea en coup de sabre and progressive facial hemiatrophy. A number of cases of morphea following the Blaschko lines on the trunk and limbs have been reported previously.1-3 However, frontoparietal morphea en coup de sabre is more clearly limited to the Blaschko lines described.4 In the case of linear morphea of the...
limbs, most cases involve broad Blaschko lines, making it more difficult to recognize a clear mosaic pattern. In our patient, the presence of morphea lesions along 1 limb, following the path of narrow Blaschko lines, supports the origin of linear morphea from cutaneous mosaicism. It is not known why the majority of cases of linear morphea reported are associated with broad Blaschko lines and only a few with narrow Blaschko lines. It may be that cutaneous mosaicism of ectodermal origin tends to follow the narrow lines whilst that of mesodermal origin tends to follow broad lines, although this correlation is not complete.5 With regard to morphea, it is likely that it is not a single disease but rather a common clinical manifestation of a number of disorders with different etiologies.

As with other patients reported in the literature, the findings in our patient support the hypothesis that linear morphea is, at least in a significant number of cases, the expression of a genetic mosaicism of a disease of probable polygenic origin. The presence of circulating antibodies6 and the existence of patients with multiple lesions of morphea and who also present linear lesions, supports the concept of mosaicism for linear morphea; those cases probably represent segmental manifestations superimposed on a polygenic disorder. The finding of this condition in patients with other collagen diseases, such as linear lupus erythematosus,7 is another argument in favor of this hypothesis.

**References**

3–23 years) and physicians would see a mean of 26 patients at each clinic (interquartile range, 24–30).

When evaluating a foot with signs and symptoms suggestive of onychomycosis (clinical estimation of the probability of onychomycosis, 80%), 25% of the respondents always confirmed the clinical diagnosis with additional tests. A further 25% confirmed the diagnosis in half of cases, and 18% sought confirmation in less than 33% of cases. On average, in a situation such as this, dermatologists confirm the diagnosis in 73% of cases. These percentages showed no correlation with the years of professional experience (divided into tertiles and using a test of association, \( P = .29 \)) or with the number of patients seen at each clinic (divided into tertiles and using a test of association, \( P = .46 \)).

Empirical antifungal treatment was started by 62% (95% confidence interval, 49%–76%) on seeing a toenail highly suggestive of onychomycosis and with negative results in the tests. This percentage also did not correlate with the years of experience (divided into tertiles and using a test of association, \( P = .82 \)) or with the number of patients seen at each clinic (divided into tertiles and using a test of association, \( P = .67 \)).

Respondents considered the following risk factors indicative of probable onychomycosis, in descending order of frequency: presence of tinea pedis (52.9%), previous history of mycosis (35.2%), diabetes mellitus (31%), immunosuppression (29.4%), presence of lesions on the fingernails (19.6%), use of public dressing-rooms (15%), and advanced age (13.7%).

According to our results, only a quarter of dermatologists always confirmed the diagnosis of onychomycosis through additional tests. When faced with suggestive lesions and negative results of the tests, 62% started systemic treatment. This approach differs from what is recommended in the clinical guidelines and usual texts. This is probably because their experience tells them that the available diagnostic tests are not sufficiently sensitive or specific, increase the cost of diagnosis, require follow-up consultations, and can lead to unnecessary treatment. Furthermore, systemic treatments are becoming increasingly safer and less expensive. This clinical problem has led to a number of studies. Effendy et al.,\(^9\) on analyzing the preliminary results of the European Onychomycosis Observatory study, found that only 39.6% of dermatologists sent samples for analysis, with a positive result in 78.1% of cases. Mehregan and Gee\(^8\) looked at the possibility of empirical treatment of all patients, but this did not appear to be a cost-effective alternative. Fletcher et al.\(^9\),\(^10\) attempted to draw up clinical diagnostic guidelines, identifying 4 clinical variables with diagnostic value.

As a limitation of our study, the sample could present a small bias as the dermatologists attending the meetings may not be representative of all dermatologists. Another possible bias could be social acceptability (a tendency to give what is considered to be the most orthodox answer); this would mean that the percentage of cases of onychomycosis that are confirmed could be even lower. This bias is minimized through the use of anonymous surveys.

The fact that dermatologists do not confirm the diagnosis of onychomycosis in all cases suggests that there is a clinical decision-taking problem that should be investigated.

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Conflicts of interest
The authors declare no conflicts of interest.

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