

CASE REPORTS

Capecitabine Induced Hyperpigmentation

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Abstract. Capecitabine is an antineoplastic agent used for the treatment of patients with metastatic solid tumors (breast and colon). Different adverse effects have been recognized, among which we find the muco-cutaneous ones and, specifically, hyperpigmentation. We report a case of localized cutaneous hyperpigmentation secondary to capecitabine in a woman that underwent surgery for breast cancer and was receiving this drug for a month. The start of therapy was associated with dysesthesia and hyperpigmentation of the hands and feet. The pathogenesis of such manifestations is unknown. Other reported cutaneous adverse effects associated with this drug involve the nails producing onycholysis, fragility, discoloration and dystrophy.

Key words: capecitabine, hyperpigmentation, breast cancer.

HIPERPIGMENTACIÓN SECUNDARIA A CAPECITABINA

Resumen. La capecitabina es un agente antineoplásico utilizado para el tratamiento de pacientes con metástasis de tumores sólidos (mama y colon) en estadio avanzado. Se reconocen distintos efectos adversos, entre los cuales se encuentran los cutáneo-mucosos y, en concreto, la hiperpigmentación. Presentamos un caso de hiperpigmentación cutánea localizada secundaria a capecitabina en una mujer intervenida de cáncer de mama y en tratamiento durante un mes con este fármaco. El inicio del tratamiento se asoció con disestesias a nivel de manos y pies, así como aumento de la pigmentación de las mismas. La etiopatogénesis de tales manifestaciones es desconocida. Otros efectos adversos descritos, desde el punto de vista dermatológico, asociados a este fármaco asientan en uñas produciendo onicolisis, fragilidad, decoloración y distrofia.

Palabras clave: capecitabina, hiperpigmentación, cáncer de mama.

Introduction

Capecitabine is an antineoplastic agent used to treat advanced, metastatic breast or colon cancer and is mostly used in patients who have not responded to standard chemotherapy.^{1,2}

The drug is known to have various adverse effects, some of which are dose dependent. Hyperpigmentation is a relatively uncommon adverse effect, occurring in approximately 3% of patients treated. The cases described to date have mainly involved black or Asian patients,³⁻⁵ and we found no reports of white patients in the literature.

We present the case of a white patient with metastatic breast cancer who developed hyperpigmentation secondary to capecitabine.

Case Description

The patient was a 46-year-old woman with skin phototype III who had been receiving treatment for alopecia areata at our department since 1997. She had responded well to topical sensitization with diphencyprone. Her medical history included breast cancer diagnosed in 1998 and treated surgically with a radical left mastectomy, followed by tamoxifen therapy.

During her last visit to our department, in May 2005, the patient reported that she had been taking capecitabine (Xeloda) for the past month for treatment of metastasis. She said that she had noticed dysesthesia and hyperpigmentation of her hands and feet since she had started taking the drug. Physical examination revealed diffuse hyperpigmentation of the palms and soles, and the effect

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Manuscript accepted for publication December 7, 2006



Figure 1. Palmar hyperpigmentation, more marked in skinfolds. Examiner's hand in the center for comparison.



Figure 2. Back of the hands, also affected by hyperpigmentation, above all in the acral areas.

was particularly noticeable in the folds of the skin (Figures 1 and 2). No hyperpigmentation was observed in the mucosa or elsewhere.

Discussion

Capecitabine is a chemotherapy drug that belongs to the fluoropyrimidine family and has the advantage that it can be administered orally. It is a prodrug of 5-fluorouracil and is converted to its active metabolite in 3 steps. Since the last step takes place in the tumor tissue, systemic toxic effects of 5-fluorouracil are minimized.⁶

It is a first-line treatment option for metastasis of solid tumors, particularly from breast or colon cancer, and can be used either alone or in combination with other drugs. It has demonstrated synergy with other chemotherapy drugs such as taxanes, with therapeutic response improvements of approximately 40% being reported.^{1,2}

Even though it is better tolerated than other antineoplastic agents, it is not devoid of adverse effects. The most common effects are gastrointestinal (diarrhea, nausea, vomiting, mucositis, and stomatitis) and hematological (neutropenia, anemia, and thrombocytopenia).^{7,8} Ocular, neurological, and dermatological toxicity are less common. The best known adverse neurological reaction is the hand-foot syndrome, also known as palmar-plantar erythrodysesthesia. It causes erythema and swelling of the hands and feet and has been described in a large proportion of patients. It is a painful, uncomfortable condition that can cause flaking or peeling of the skin and ulceration if treatment is not withdrawn or reduced.

Our patient developed both hyperpigmentation and hand-foot syndrome. Was this a coincidence or could pigmentary changes be a form of onset of the syndrome? Opinions in this respect vary considerably. While some

authors believe that hyperpigmentation may be part of the onset of hand-foot syndrome, others believe that their coexistence only occurs by chance. Narasimhan et al³ described the coexistence of hyperpigmentation and hand-foot syndrome in 3 black patients. It is now well established that hyperpigmentation is both more common and more severe in black patients than in patients from other ethnic groups. The pigmentary changes can be generalized, affecting skin and mucosa all over the body,^{3,5} or, as was the case with our patient, restricted to the palms and soles.³

Many chemotherapy agents have been linked to increased skin pigmentation.⁹ The following mechanisms of action have been described:

1. Direct stimulation of melanogenesis in the melanocytes (doxorubicin, bleomycin, and busulfan)
2. Postinflammatory hyperpigmentation secondary to increased photosensitivity (methotrexate)
3. A combination of both mechanisms (cyclosporine and 5-fluorouracil)

Hyperpigmentation of the skin induced by 5-fluorouracil occurs in approximately 5% of patients and is more common when the drug is administered intravenously.¹⁰⁻¹² It affects both light-exposed areas, via a mechanism involving photosensitization, and unexposed areas. Given that capecitabine is a prodrug of 5-fluorouracil, it would seem logical to assume that both drugs could lead to similar adverse reactions. The etiology of these reactions is unknown, particularly in the case of hand-foot syndrome.

Capecitabine is also reported to affect the nails in the form of onycholysis, photoonycholysis,⁴ fragility, discoloration, and dystrophy.¹³

Given that the drug is being increasingly used, thanks to its clinical efficacy and ease of administration, we believe

that increased awareness of its adverse effects among dermatologists and oncologists will facilitate improved management.

Conflicts of Interest

The authors declare no conflicts of interest.

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