KIT Mutations in a Series of Melanomas and Their Impact on Treatment With Imatinib☆

Mutaciones en KIT en una serie de melanomas y repercusiones en el tratamiento con imatinib

The first studies on the use of imatinib in patients with metastatic melanoma were published in 2005 and 2006 and reported that the drug was not effective in this setting.[1,2] However, a study published in 2006, which analyzed 102 primary melanomas, described *KIT* mutations or copy number increases in 39% of mucosal melanomas, 36% of acral melanomas, and 28% of melanomas arising on chronically sun-damaged skin, but in 0% of those arising on skin without chronic sun damage.[3] In addition to isolated cases in which patients with metastatic melanoma who had *KIT* mutations achieved partial or complete regression with imatinib,[4,5] results were recently published of 2 series of patients with metastatic melanoma who received imatinib after their tumors were found to contain genetic alterations (mutations or amplifications) in *KIT*.[6,7] Carvajal and coworkers[6] achieved an overall durable response rate of 16% in a group of 25 patients. In a group of 43 patients of Asian origin, Guo and coworkers[7] reported a disease control rate of 53.5% (partial response in 10 patients and stable disease in 13). In a recent publication in The Lancet, Romano and colleagues[8] reported that, based on their experience at Memorial Sloan-Kettering Cancer Center, mutations in exons 11 and 13 of *KIT* better predict response to imatinib treatment than do amplifications in this gene.[8] Several studies have demonstrated that the mere immunohistochemical expression of KIT does not correlate with response to imatinib.

Given the limited experience with imatinib in the treatment of metastatic melanoma, we believe it is important to present our data concerning the frequency of *KIT* mutations (Table 1), and our results describing the response to imatinib of a small group of patients with confirmed mutations. We present the case of a patient treated with imatinib who achieved a temporary partial response in the form of a reduction in the number and size of visceral metastases. The key data for 2 other patients treated with imatinib are summarized in Table 2.

The present case report concerns patient number 1. The patient was a 49-year-old man with melanoma of the penis (9 mm Breslow thickness, ulceration, and 6 mitoses/mm^2) and multiple bilateral inguinal-iliac metastases (stage IIIC; pT4b, N3, M0). After surgical treatment, the patient commenced adjuvant therapy with high-dose interferon. After 7 months of interferon treatment, skin metastases were observed in the scrotum, the lung, and the lymph nodes of the left groin. The disease progressed after two lines of chemotherapy (dacarbazine followed by carboplatin). At this point, analysis of *KIT* in the patient's tumor using molecular biology techniques identified a mutation in exon 11, for which the patient was treated with imatinib (400 mg twice a day). In the course of the disease, progressive increases were observed in the levels of S100 (up to 2.49: normal value, < 0.4 μg/L) and lactate dehydrogenase (LDH) (up to 434: normal value, 100-250 U/L). After 1 month of treatment with imatinib, clinical observation revealed a partial response of the skin lesions and lymph nodes, normalization of S100 levels (0.22), and a decrease in LDH levels (303). A computed tomography scan 3 months later also identified a partial response of the lung metastases (Fig. 1). However, 3 months later further increases in S100 (0.71) and LDH (378) were observed and 4 weeks later progression of lung disease and new metastases of the mediastinum were confirmed. The patient was treated as a last resort with ipilimumab. Several weeks later, multiple metastases were detected in the central nervous system and treated with palliative radiotherapy and systemic corticosteroids; the patient died 2 months later.

In view of our results (temporary partial response, a lasting stabilization of disease, and eventual progression), we believe that drugs that act by inhibiting KIT should be evaluated in patients with melanoma in whom disease has progressed despite conventional chemotherapy and in those with *KIT* mutations. Our results confirm the finding of other groups that this mutation occurs in acral and mucosal melanoma. Although one of the melanomas in which we detected a *KIT* mutation corresponded to a superficial spreading melanoma, the tumor was located on the forehead of a 55-year-old patient with moderate solar elastosis. While acral and mucous melanomas are relatively infrequent, they do not usually harbor *BRAF* mutations and thus are not susceptible to

Table 1 Results of the Molecular Analysis of *KIT* Status in 56 Patients with Melanoma by Site and Histological Type.

	No KIT Mutation	KIT Mutation (Exon)
Location	51	5
Head and neck	8	1 (11)
Upper extremities	4	
Trunk	14	
Lower extremities	8	
Hands and feet	12	2 (1 in 11, 1 in 13)
Mucosae	4	2 (1 in 11, 1 in 13)
Unknown primary	1	
Histological Type		
Lentigo maligna melanoma		
Superficial spreading melanoma	18	1 (11)
Nodular	18	
Acral lentiginous	7	2 (1 in 11, 1 in 13)
Mucosal	4	2 (1 in 11, 1 in 13)
Other	4	

DNA was extracted from the primary tumor or, when this was not possible, from any other metastatic implant, and sequencing was performed on exons 9, 11, 13 and 17.

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Table 2 Summary of Clinical History and Response to Imatinib Treatment in Patients 2 and 3.

	Primary Melanoma	Spread	Course	*KIT*	Imatinib Treatment
Patient 2	Acral lentiginous malignant melanoma, Breslow thickness 7 mm, ulcerated, sole of right foot, with satellitosis	Metastases in 8 lymph nodes in the right groin	Adjuvant high-dose interferon. Cutaneous recurrence at 5 months	Mutation in exon 11	Imatinib 400 mg/12 h. Diarrhea, adjusted to 400 mg in the morning and 200 mg in the evening
Female, 72 years		Stage IIIC (T4b, N3, M0)	Imiquimod + dacarbazine Cutaneous progression at 8 months Temozolomide Visceral spread (lung, liver) at 6 months		Stable disease in lung and liver with a decrease in the size and number of cutaneous metastases up to the present (11 months)
Patient 3 Female, 38 years	Ulcerated perianal malignant melanoma, Breslow thickness 22 mm	Regional lymph node metastases, lung and liver (stage IV)	Dacarbazine Progression after 2 months	Mutation in exon 13	Imatinib 400 mg/12 h.
					Progression at 3 months. Palliative radiotherapy. Death 3 months later

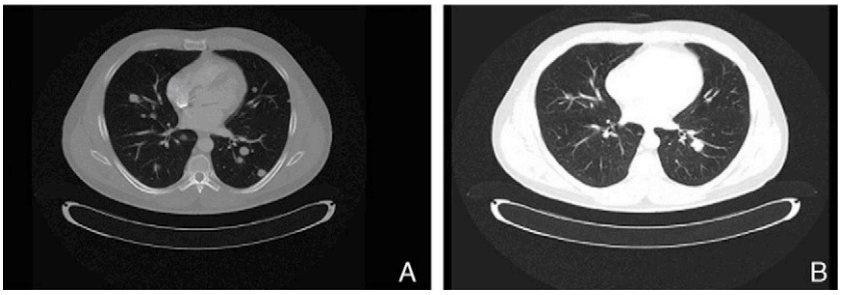

Figure 1 Disappearance of most of the lung metastases following 3 months of imatinib therapy in patient no. 1. A, Computed tomography (CT) scan performed on November 23, 2009, prior to treatment. B, CT scan performed on March 2, 2010, after 3 months of treatment with imatinib.

treatment with the new inhibitors of this tyrosine kinase, such as vemurafenib. Thus, confirmation of a *KIT* mutation opens the door to an additional treatment option for this group of melanomas. In the near future, these new KIT inhibitors, used both alone and in conjunction with traditional chemotherapy, will likely improve upon the results achieved to date.

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Cutaneous Infection in a Tattoo Due to *Mycobacterium Chelonae*: A Report of 2 Cases and a Review of the Literature☆

Infección cutánea por *Mycobacterium chelonae* en un tatuaje. Presentación de 2 casos y revisión de la literatura

Skin complications arising from tattoos include contact dermatitis, photodermatosis, lichenoid reactions, granulomas (foreign body, sarcoid), and infection.[1,2] Small outbreaks of skin infections due to *Mycobacterium chelonae* in contaminated tattoo ink have recently been reported.

Patient 1

Patient 1 was a 33-year-old man who had had a tattoo placed on his right leg 4 years previously. Three months before consulting, he had the shield outlined in black and a gray flame added. Asymptomatic lesions appeared 2 weeks later and were treated unsuccessfully with topical corticosteroids and antibiotics. The patient was then referred to the dermatology department.

Physical examination of the gray flame revealed several papulopustules measuring 1 mm to 4 mm in diameter (Fig. 1A). The border drawn in black ink the same day was not affected. Analysis of a biopsy specimen revealed granulomas with abscess formation (Fig. 1B); Kinyoun staining was negative. *M chelonae* grew in culture 15 days later. The chest x-ray was normal, and laboratory tests (including serology for HIV and hepatitis) were negative. The patient was treated empirically with clarithromycin (500 mg/12 h) for 3 months. The lesions disappeared.

Patient 2

Patient 2 was a 25-year-old woman who had had a black and grey tattoo placed on the dorsum of the foot 5 months previously by the same tattoo artist. Five days later, an asymptomatic lesion appeared on the gray areas. The lesion had been treated unsuccessfully with topical antibiotics and corticosteroids. Physical examination revealed an erythematous plaque measuring 1 cm in diameter that was soft to palpation with occasional pustules on its surface (Fig. 2A). Analysis of a biopsy specimen revealed granulomas with abscess formation; Kinyoun staining showed a small accumulation of acid-alcohol-fast bacteria (Fig. 2B), but culture was negative. The patient was treated with clarithromycin (500 mg/12 h), although the drug was withdrawn in less than a month because of digestive tract intolerance. As the lesion had disappeared, no further treatment was administered.

Discussion

M chelonae is a fast-growing saprophytic mycobacterium that is found in tap water and water tanks and can contaminate surgical material. Skin infections have been reported in surgery, acupuncture, mesotherapy, and tattooing. In the case of tattoos, the infections affect the gray areas, as nonsterile water is added to the black ink.

The first case of a tattoo infected by mycobacteria was reported in 2003. Diagnosis was based on Ziehl-Neelsen staining and positive results in polymerase chain reaction (PCR) analysis. De Quatrebarbes et al[4] later reported the first epidemic of *M chelonae* in tattoos. Twenty men presented with a rash in the gray area of their tattoos 7 to 10 days after having them performed by the same artist. Culture was positive for *M chelonae* in 13 patients.[4] Goldman et al[5] subsequently included these patients in a letter reporting on 48 patients who were tattooed by 2 different artists in Le Havre, France. *M chelonae* was found in 2 bottles of diluted black ink. New cases have since been reported in France,[6] Australia,[7] and the United States.[8,9] Rodríguez-Blanco et al[10] recently reported 5 cases in La Coruña, Spain; 3 were culture-positive and 2 PCR-positive. Table 1 summarizes the cases published to date.

All the cases involved the appearance of papulopustules in the gray areas of the tattoo 1 to 2 weeks after placement. No systemic involvement was recorded. The diagnostic delay (1-5 mo) is noteworthy, as the patients were initially diagnosed with an allergic reaction or bacterial infection and were treated with topical antibiotics, corticosteroids, or both. No standard treatment has been defined, although the most widely used agent is clarithromycin, which, according to Drage et al,[8] should be prescribed for at least 6 months; however, digestive tract intolerance makes this difficult.[10] Some clinicians have combined clarithromycin

☆ Curcó N, et al. Infección cutánea por Mycobacterium chelonae en un tatuaje. Presentación de 2 casos y revisión de la literatura. Actas Dermosifiliogr. 2012;103:842-5.