



Figure 1. A-C). Study patient at the start of ustekinumab treatment after failure of the first and second-line biological therapies (etanercept and adalimumab). D) PASI 90 response after 12 weeks of 45 mg of ustekinumab.

44 patients were controlled under ustekinumab (PASI < 3) with a mean follow-up of 22.1 months and no severe AE. In contrast to initial studies [3, 4], previous failure to one or more TNF α -inhibitors did not influence the therapeutic response to ustekinumab. In our study, a PASI 75 (or higher) response was achieved in 83.5% of non-anti-TNF α naive patients treated with ustekinumab as a second, third, or fourth-line therapy. Hence, we observed a PASI 75 response at 12 weeks, comparable to the response achieved in the initial clinical trials of ustekinumab given to naive patients [3, 7]. Additionally, in our study, the treatment response was not influenced by the number of previous anti-TNF α treatments, and was sustained for the majority (89.8%) of patients. Finally, the AE profile appeared more favourable with ustekinumab, possibly due to non-interference with the macrophage/granuloma mechanism [8].

Switching from ustekinumab was necessary in five patients. Remarkably, all of those who switched had psoriatic arthritis and two were obese; two prognostic factors associated with poor treatment response [9, 10]. The two patients who switched due to primary inefficacy did not achieve response endpoints with secukinumab (however, the follow-up period was short). This suggests the existence of different inflammatory pathways driving the disease and resistance mechanisms. Their clarification may unravel new treatment targets for refractory patients.

We acknowledge the inherent limitation of the small sample size of our study with data retrospectively collected from registries. However, our efficacy data are relevant, considering that the majority of patients had severe disease, refractory to two or three biological treatments, and it refers to real-life comorbid patients.

In conclusion, our study suggests that ustekinumab is a good option for severe psoriasis refractory to one or more anti-TNF α agents, leading to good and sustained responses regardless of the number of previous therapeutic lines. Ustekinumab may be a first-line option after failure of an anti-TNF α agent in order to optimize response and minimize costs of switching strategies. ■

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B-cell lymphomatoid contact dermatitis caused by methylisothiazolinone and methylchloroisothiazolinone

The clinical and histological expression of allergic contact dermatitis may resemble a cutaneous B- or T-cell lymphoma, such as “lymphomatoid contact dermatitis”. This entity was first described in 1976 by Orbaneja *et al.* [1], and is chronic and persistent allergic contact dermatitis, which is included in the class of cutaneous lymphoid hyperplasias, a mixed group of benign T- or B-cell lympho-proliferative disorders with clinical and histological features resembling true lymphoma [2]. As stated by Wall [3], “the term *lymphomatoid contact dermatitis* should refer to cases where the lymphomatoid reaction is in areas of contact with positively reacting allergens, clearing with avoidance of the allergen”.

A 56-year-old male presented in 2013 with a 10-year history of persisting, progressively accumulating itching plaques and subcutaneous nodules, initially located at the sternum

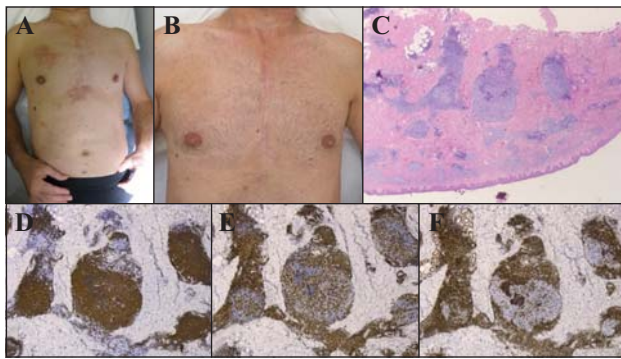


Figure 1. **A)** Two large deep-red and slightly infiltrated plaques on the sternum and right upper thorax; some smaller subcutaneous nodules are also scattered over the abdomen. **B)** Avoidance of products containing MI and MCI resulted in marked improvement and remission of the lesions. **C)** Slight acanthosis in the epidermis, with a mixed B- and T-cell infiltrate with lymphocyte follicles in the dermis (haematoxylin-eosin; original magnification x25). **D, E, F)** Immunohistochemistry showing abundance of CD20-positive B-lymphocytes (**D**) in the germinal centres with some CD3-positive T-lymphocytes (**E**); Bcl2 staining in the germinal centre is negative (**F**) (immunostain; magnification: x50).

and progressively expanding to the right upper thorax, with some scattered lesions on his abdomen (figure 1A). He had received coronary artery bypass grafting (CABG) in 2003, for which an iron wire for sternal closure had been used, being the site of the first plaque.

Different treatments, including topical corticosteroids and systemic antibiotics, had been ineffective. Several biopsies taken by a private dermatologist had shown varying and inconclusive results.

A new biopsy in 2014 showed histological evidence for a possible B-cell lymphoid hyperplasia (figure 1C-F), however, PCR analysis for clonal B-cell rearrangement did not reveal clonality, which invalidated the diagnosis of B-cell lymphoma. Further blood investigations, including immune phenotyping and computerized tomography of the thorax and abdomen, did not indicate any extra-cutaneous signs of malignancy either.

To exclude a drug-induced pseudolymphoma, all medications were switched to chemically non-related analogues, and systemic steroid treatment was installed which produced partial lesion regression (>50%), but no further improvement with tapering of the dose.

Patch testing was performed in September 2015 with the European baseline series and a metal series (Chemotechnique Diagnostics, Vellinge, Sweden), which resulted in positive reactions to methylisothiazolinone (MI) and the mixture of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) only (table 1). Both MI and MCI were identified in a shampoo the patient was presently using and in two household detergents that he weekly handled. MI was also found in a previously used shampoo. Avoiding contact with these products resulted in marked improvement of the lesions at the follow-up consultation in November 2015, and disappearance of his lesions by January and February 2016, except for some occasional itching (figure 1B). This indicates a clear rela-

Table 1. Patch test results to methylisothiazolinone (MI), methylisothiazolinone/methylchloroisothiazolinone (MI/MCI), and methylchloroisothiazolinone (MCI).

	D2	D4	D9
European baseline series			
MI 500 ppm	+	+	++
MI 2000 ppm	++	+++	+++
MCI 0.015% aq.	+	+	NR
MI/MCI 100 ppm	?	+	+(D7)
MI/MCI 200 ppm	+	+++	+++
Metal series			
	-	-	-

tionship between avoidance of exposure to MI/MCI and disappearance of the skin lesions.

We thus considered the diagnosis of lymphomatoid contact dermatitis induced by MI and MI/MCI present in his shampoos and detergents (possibly an airborne factor) as most likely. The CABG region, being affected first, might perhaps be related since this is a “locus minoris resistentiae”. MI and MI/MCI are widely used in industrial and household products and cosmetics, and are currently the most prevailing causes of contact allergy associated with preservatives in Europe [4]. T-cell lymphomatoid contact dermatitis from MI/MCI has been published [5-7], also with airborne features [7]. Here, we describe the first case of B-cell lymphomatoid contact dermatitis from MI/MCI.

Long-term follow-up is required because pseudolymphomas may occasionally develop into true lymphomas [8] or leukaemias [9]. ■

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Vitamin D levels in a cohort of Portuguese melanoma patients relate to time of follow-up from diagnosis, sun-exposure behaviour, and use of photoprotection

Patients with a personal history of melanoma have been recognized as a group at risk of vitamin D deficiency, since they are instructed to adopt sun avoidance measures and photoprotection [1]. Although Portugal is one of the sunniest European countries, this sun-avoiding behaviour may lead to vitamin D deficiency during the years following diagnosis. However, data concerning 25-hydroxyvitamin D3 [25(OH)D] levels during follow-up are lacking.

We aimed to study the serum 25(OH)D levels in a cohort of Portuguese patients with a previous diagnosis of melanoma, and to determine any relationship with follow-up time, sun-exposure behaviour, and use of photoprotection. Serum levels of 25(OH)D were measured in consecutive patients followed for melanoma consultation at our department (Lisbon, latitude 38°) over four months (January-April). Patients already on vitamin D supplementation were excluded. Sun-exposure behaviour after the diagnosis was classified as “avoiding behaviour” or “no particular restriction”, according to clinical history of beach and outdoor activities. Use of photoprotection was classified as “rare/irregular” or “regular”, according to how often the patient used sunscreen with SPF $\geq$ 50. Based on international recommendations [2], the serum 25(OH)D level was categorized as “sufficient” ($\geq$ 30 ng/mL), “insufficient” (20-29.9 ng/mL), or “deficient” ($<$ 20 ng/mL).

Eighty-six patients with 104 melanomas were included, of whom 53.5% were female. The mean age at the time of diagnosis was 56.4 ± 16.8 years. The mean follow-up time after the diagnosis of the first melanoma was 7 ± 5.2 years (range: 0.4-21 years). Breslow thickness was below 0.75 mm in 90 melanomas (86.5%). Skin phototype II, III and VI were observed in 41 patients, 44 patients, and one patient, respectively. The average serum 25(OH)D level was 16.5 ± 8.1 ng/mL (range: 4.8-41.9 ng/mL). Eighty-one patients (94.2%) had suboptimal values: 62 (72.1%) deficient and 19 (22.1%) insufficient levels.

Fifty-four patients (62.8%) reported regular use of very high photoprotection and 53 (61.7%) avoided sun exposure (table 1). Serum 25(OH)D levels were significantly lower in patients followed for more than six years ($p = 0.023$), patients with regular use of very high-level photoprotection ($p = 0.029$), and patients avoiding sun exposure ($p = 0.006$). In these three groups, there were significantly more patients with vitamin D deficiency (table 1).

Concerning Portuguese data on serum 25(OH)D levels, there are only a few non-melanoma-related studies [3-6]. In two studies [4, 6], analysis of 25(OH)D measurements performed for any given reason at a hospital revealed suboptimal values in 80.7-88.1% and deficiency in 60-65%. In a cohort of elderly patients admitted to an internal medicine ward, 92.7% had 25(OH)D deficiency [5]. Our study is the first concerning Portuguese melanoma patients and shows the high frequency of suboptimal 25(OH)D values (94.2%) and deficiency (72.1%) in this subgroup. These values are higher than those of the above-mentioned studies which included patients with diseases affecting calcium and parathyroid hormone levels, and are only exceeded by the elderly functionally-impaired cohort of Santiago *et al.* [5].

Previous European studies concerning 25(OH)D levels in melanoma patients during follow-up were performed in the United Kingdom [1], Scotland [7], and Spain [8]. In the United Kingdom, deficiency was found in 55% after one year of follow-up, with no seasonal variations [1]. In Scotland, deficiency was found in 47.6% in September/November, after an unknown period of follow-up, with some patients taking vitamin D supplementation [7]. In Spain, 81.5% of the patients had suboptimal values in autumn/winter, also after an unknown period of follow-up [8]. Our cohort shows an even higher proportion of patients with 25(OH)D deficiency and insufficiency, after an average of 7 ± 5.2 years of follow-up. Curiously, Portugal has more sunlight hours and higher UV index averages than other European countries.

The size of the sample might have been a limitation regarding the robustness of the study. Another limitation of our study was an absence of baseline levels at diagnosis which could have been compared with levels during follow-up. However, our results show that patients with more than six years of follow-up have significant lower 25(OH)D levels. In conclusion, melanoma patients have a high risk of vitamin D deficiency that might be aggravated during follow-up even in sunny countries, due to their sun-avoiding and photoprotection behaviours, in agreement with medical advice. In order to avoid the well-established detrimental bone effects of vitamin D deficiency, together with the possibility that melanoma patients with lower 25(OH)D levels may have worse outcomes [9], the routine determination of 25(OH)D in these patients should be implemented at initial diagnosis, followed by oral supplementation, if suboptimal levels are detected, and additional monitoring [10]. ■

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