patients reacted to foods containing the hydrolyzed protein. The reason for this finding seems to be that hydrolysis entails the appearance of new epitopes, which are responsible for the allergic reaction.[1]

We present a new case in order to make this disease more widely known and to help direct the patient towards appropriate diagnostic tests.

We stress the importance of performing patch tests using the patient's own products, since in cases such as ours, tests using standard panels could yield false-negative results. Diagnostic testing in patients with contact urticaria should be performed with the utmost caution and in a specialized center with full resuscitation facilities. The product should be applied first in an open test; if the result is negative, a prick test should be performed before the closed patch tests. Ours is the first reported case in which both patch tests and the prick test were positive, indicating that the same agent could cause both immediate and delayed hypersensitivity, thus explaining the occurrence of eczema and contact urticaria in the same patient.

Collaboration with the allergology department is important in order to detect sensitization or cross-reactivity with other cereals and thus prevent reactions to foods.

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Lack of High-Quality Evidence On the Value of Sentinel Node Biopsy in Melanoma☆

Falta de evidencia de calidad sobre el valor de la biopsia del ganglio centinela en melanoma

To the Editor:

It was with great interest that we read the very sound and relevant opinion article published in a recent issue of *Actas Dermo-Sifiliográficas* on sentinel node biopsy (SNB) in malignant melanoma.[1] We believe that SNB may have a minor impact on overall survival, but that such an impact has yet to be demonstrated. Currently, however, there is no high-quality evidence to determine whether this is indeed the case.

The results of the only randomized clinical trial to analyze the therapeutic value of SNB in malignant melanoma, the Multicenter Selective Lymphadenectomy Trial (MSLT-I),[2] were clear: there were no differences in overall survival between the SNB group and the observation group ($P = .59$). Since the randomization of patients is what minimized the differences between the 2 groups and allowed them to be compared, the postrandomization analysis through which the authors attempt to reach the statistical significance that their study lacks introduces a classification bias that invalidates its conclusions. All patients with clinical and radiologic evidence of disease recurrence in the observation group had evident lymph node disease. This was not the case in the group with tumor-positive sentinel nodes (SNs), in which perhaps as many as 25% of patients may have been false positives. The existence of this 25% of false positives can be demonstrated through simple mathematical analysis[3]: there was a higher incidence of lymph node disease in the SNB group than in the observation group. It has been argued that there were cases of late recurrence in the observation group,[4] but this was the case in the SNB group as well (20% were false negatives). Furthermore, the fourth interim analysis of the MSLT-I indicated that the rate of late recurrence had slowed down and that it was practically impossible for

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the rate of nodal recurrence in the observation group to equal that of the SNB group.[3]

It was also been rightly pointed out that the impact of SNB on overall survival decreases over time.[4] A 20% survival benefit for the SNB group with respect to the proportion of patients with lymph node disease (16%) would mean an increase in overall survival for the entire cohort of only 3.2% (20% of 16%). Calculation of the sample size needed to detect such a difference with a power of 80% and randomization in a 40:60 ratio (as in MSLT-I) using Ene software v. 2.0 (Glaxo-Smith-Kline, Madrid, Spain) for the comparison of independent proportions in a bilateral contrast test shows that nearly 4000 patients would be needed: 1575 in the control group and 2364 in the intervention group. The power of the study of Morton et al,[2] with 2001 patients, was less than 40%.

Additionally, the Australian authors who recruited 946 of the 2001 patients for MSLT-I performed lymphoscintigraphy in the observation group outside the protocol,[5] thus introducing a further bias. They located the SN and without removing it tattooed the skin to permit close clinical and ultrasound monitoring. While they did observe recurrence in the SNs they had detected, they undermined the main objective of the study through early diagnosis and treatment, reducing the overall survival advantage of the SNB group.

In short, not only are there ''certain doubts'' about the therapeutic value of SNB in melanoma, as Dr. Botella[1] maintains, but there is also a complete lack of quality evidence. The only randomized clinical trial to date that has attempted to analyze its value was clearly underpowered and had proven biases. In view of this lack of evidence, almost all guidelines (National Comprehensive Cancer Network, European Organisation for Research and Treatment of Cancer [EORTC], Australian, etc) recommend discussing SNB with patients and offering it as an option rather than simply indicating the need for the procedure. The point made concerning the extension of the indications for selective lymphadenectomy[1] thus seems pertinent and its use in tumors with a thickness of at least 0.75 mm in the presence of mitosis is prudent.

Our group has been performing SNB in cases of malignant melanoma since 1999 and we continue to offer it because it allows early treatment of lymph node disease and better risk classification. Unfortunately, a positive SN is indicative of a poor prognosis and no treatment has been shown to improve it. The Sunbelt Melanoma Trial found no benefit in interferon treatment in patients with a positive SN.[6] The benefits of early lymphadenectomy after detection of a positive SN compared to waiting for clinical or radiologic recurrence has yet to be determined (MINITUB and MSLT-II). Many patients prefer watchful waiting following detection of a positive SN,[7] given that in more than 80% of cases no other affected nodes will be found at lymphadenectomy and that the significant morbidity associated with the procedure can thus be avoided.

This conservative attitude on the part of patients stands in contrast to the position taken by authors whose standard of care is complete lymphadenectomy for micrometastases of a single lymph node,[8] especially now that the new American Joint Committee on Cancer staging criteria set no lower limit for considering a SN to be positive, thus giving rise to the new concept of ''submicrometastasis''. A review carried out in 2011 by authors of the same group[9] minimizes the importance of the false negatives and does not even discuss the false positives, providing an idealized view of SNB. Since the 1990s the management of nodal involvement in malignant melanoma has been more aggressive in the United States than in Europe.[10] The EORTC group are currently investigating less invasive techniques. They evaluate nodal tumor burden as part of their decision-making process and consider ultrasound as an alternative or complement to SNB.[11] This approach should guide our clinical practice until we have more evidence from MINITUB and MSLT-II, the 2 clinical trials currently underway.

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