

**Fig 2.** Perineural squamous cell carcinoma: Another case of frozen sections stained with toluidine blue. **A**, The perineural corona sign is prominent at the 40× magnification. **B**, At the 100× magnification, the actual nerve involvement becomes more obvious.

poor, with less than 35% of patients surviving for 5 years.<sup>4</sup> Given the aggressive nature of perineural SCC, the development of efficient and easily applicable techniques to diagnose subtle perineural invasion is of paramount importance.

The perineural corona sign can enhance the diagnostic accuracy for perineural SCC. Occasionally, we encounter the distinctive stromal changes without obvious perineural tumor cells. Asymmetric tumor spread along the nerve can create a skiplike phenomenon and can result in false-negative margins during MMS.<sup>5</sup> The finding of a perineural pink corona, even in the absence of tumor cells, may be a harbinger of perineural invasion and should prompt the Mohs surgeon to consider further tissue evaluation.

We propose that toluidine blue could be used alone or in conjunction with hematoxylin and eosin stain when performing MMS for clinically high-risk SCCs to aid in the recognition of perineural SCC. Toluidine blue is a fast and reliable stain that can be easily incorporated in any Mohs practice. The perineural corona sign can advantageously highlight subtle or nearby perineural involvement.

*Anna Drosou, MD, Diane Trieu, MD, Leonard H. Goldberg, MD, and Arash Kimyai-Asadi, MD*

*Derm Surgery Associates, Houston, Texas*

*Funding sources: None.*

*Conflicts of interest: None declared.*

*Correspondence to: Anna Drosou, MD, 7515 Main, Suite 240, Houston, Texas 77030*

*E-mail: [anndros@yahoo.com](mailto:anndros@yahoo.com)*

## REFERENCES

1. Jimenez F, Grichnik J, Buchanan M, Clark R. Immunohistochemical techniques in Mohs micrographic surgery: their

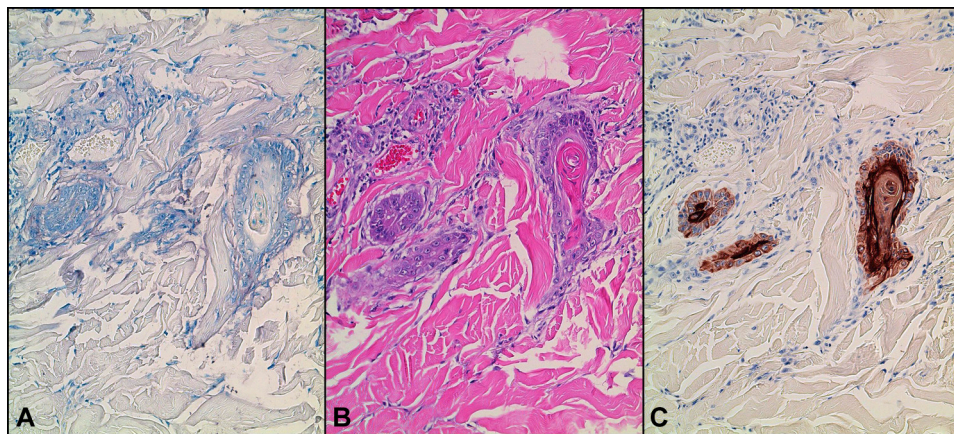
potential use in the detection of neoplastic cells masked by inflammation. *J Am Acad Dermatol* 1995;32:89-94.

2. Birkby CS, Whitaker DC. Management considerations for cutaneous neurophilic tumors. *J Dermatol Surg Oncol* 1988; 14:731-7.
3. Huphreys TR, Nemeth A, McGrevey S, Baer SC, Goldberg LH. A pilot study comparing toluidine blue and hematoxylin and eosin staining of basal cell and squamous cell carcinoma during Mohs surgery. *Dermatol Surg* 1996;22:693-7.
4. Powe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis and survival rates in squamous cell carcinoma of the skin, ear and lip. Implications for treatment modality selection. *J Am Acad Dermatol* 1992;26:976.
5. Matorin PA, Wagner RF. Mohs micrographic surgery: technical difficulties posed by perineural invasion. *Int J Dermatol* 1992; 31:83-6.

<http://dx.doi.org/10.1016/j.jaad.2014.04.076>

## Enhancing techniques to evaluate tumor margins

*To the Editor:* Drosou et al describe a quick and straightforward technique for detecting perineural invasion in squamous cell cancers (SCCs) using toluidine blue.<sup>1</sup> Toluidine blue has been historically used by Mohs surgeons for its capacity to highlight mucinous stroma around basal cell carcinomas (BCCs). However, over the years this has been largely replaced by the use of rapid hematoxylin and eosin (H&E) stains due to improved cellular and histologic definition. Finding individual tumor cells, especially in small localized areas such as around nerves or blood vessels or in heavily inflamed areas, can be very challenging. The toluidine blue sign noted by Drosou et al appears very useful for suggesting the presence of tumor. However, immunohistochemical stains offer improved specificity and enhanced contrast, allowing easier detection of tumor cells (Fig 1). The use of immunohistochemistry for Mohs micrographic surgery (MMS) has long been established and a recent survey shows that



**Fig 1.** Comparison of tissue staining techniques. Toluidine blue (A), hematoxylin and eosin stain (B), pan anticytokeratin immunohistochemistry (C) for an infiltrative squamous cell carcinoma. Formalin fixed paraffin embedded (FFPE) tissue was used for this example.

immunostaining in Mohs surgery has nearly doubled in the past decade.<sup>2</sup> Jimenez et al showed that anticytokeratins help reveal the presence of tumor cells in dense inflammatory aggregates as well as highlight perineural involvement in several cases of SCC.<sup>3</sup> Variants of SCC, such as spindle cell carcinomas, which are notoriously difficult to identify with standard stains, are also easier to identify with the use of immunohistochemical markers. Dermatofibrosarcoma protuberans (DFSP) tumors may be more readily traced with markers such as CD34, and markers such as BerE4 and MART-1 can be used for BCC and lentigo maligna, respectively.<sup>4-6</sup> Immunohistochemical protocols do take more time, but they have become more efficient and readily available for everyday use. For instance, a cytokeratin (AE1/AE3) immunostaining protocol as short as 19 minutes can be used for the detection of SCC tumor cells in Mohs frozen sections.<sup>7</sup> In the future, this may be further improved by using immunofluorescence, which offers the added benefit of not only viewing specimens with an incredible amount of visual contrast but also gives the Mohs surgeon the ability to view several cellular markers simultaneously. Drosou and colleagues offer a quick and important sign that is useful in identifying perineural invasion in SCC. Other approaches such as “immuno MMS” should also be considered when difficult cases are identified to maximize the clearance of margins.

Titilola Sode, BA,<sup>a</sup> Theresa Cao, DO,<sup>a</sup> George W. Elgart, MD,<sup>a</sup> Francisco Jiménez-Acosta, MD,<sup>b</sup> and James M. Gricchnik, MD, PhD<sup>a</sup>

Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of

Medicine,<sup>a</sup> Florida; Dermatological Private Practice, Las Palmas de Gran Canaria,<sup>b</sup> Spain

*Funding sources: Anna Fund Melanoma Program, Sylvester Comprehensive Cancer Center, Frankel Family Division of Melanocytic Tumors, Department of Dermatology and Cutaneous Surgery, and benefactors, especially William Rubin and his family and friends.*

*Disclosures: Dr Gricchnik has consulted for Roche, Novartis, and Caliber ID and is a DigitalDerm major shareholder. Drs Cao, Jiménez-Acosta, and Elgart, as well as author Sode have no potential conflicts of interest to declare.*

*Correspondence to: James M. Gricchnik, MD, PhD, Department of Dermatology and Cutaneous Surgery, BRB Room 912, 1501 NW 10th Ave, Miami, FL 33139*

*E-mail: [Gricchnik@miami.edu](mailto:Gricchnik@miami.edu)*

#### REFERENCES

1. Drosou A, Trieu D, Goldberg L, Kimyai Asadi A. The perineural corona sign: enhancing detection of perineural squamous cell carcinoma during Mohs micrographic surgery with toluidine blue stain. *J Am Acad Dermatol* 2014;71:826-7.
2. Trimble JS, Cherpelis BS. Rapid immunostaining in Mohs: current applications and attitudes. *Dermatol Surg* 2013;39(1pt1):56-63.
3. Jimenez FJ, Gricchnik JM, Buchanan MD, Clark RE. Immunohistochemical techniques in Mohs micrographic surgery: their potential use in the detection of neoplastic cells masked by inflammation. *J Am Acad Dermatol* 1995;32:89-94.
4. Jimenez FJ, Gricchnik JM, Clark RE. CD34-positive spindle cells in nerves. *J Cutan Pathol* 1994;21:189-90.
5. Jimenez FJ, Gricchnik JM, Buchanan MD, Clark RE. Immunohistochemical margin control applied to Mohs micrographic

- surgical excision of dermatofibrosarcoma protuberans. *J Dermatol Surg Oncol* 1994;20:687-9.
6. Kelley LC, Starkus L. Immunohistochemical staining of lentigo maligna during Mohs micrographic surgery using MART-1. *J Am Acad Dermatol* 2002;46:78-84.
7. Cherpelis BS, Turner L, Ladd S, Glass LF, Fenske NA. Innovative 19-minute rapid cytokeratin immunostaining of nonmelanoma skin cancer in Mohs micrographic surgery. *Dermatol Surg* 2009;35:1050-6.

<http://dx.doi.org/10.1016/j.jaad.2014.05.043>

### Comments on "Diet and psoriasis, part I: Impact of weight loss interventions"

*To the Editor:* We read with great interest the review on weight loss in psoriasis recently published online in the Journal.<sup>1</sup> The authors concluded that weight loss may be a useful preventive and adjunctive therapy for the treatment of psoriasis but "larger, prospective clinical studies are needed to further delineate the efficacy of diet and weight loss interventions in psoriasis improvement." We have recently completed a randomized clinical trial on weight reduction in overweight or obese psoriatic patients.<sup>2</sup> The study included patients with chronic plaque psoriasis, aged 18 to 80 years, with body mass index 25 or higher and a Psoriasis Area and Severity Index (PASI) score of 10 or higher, who had started a systemic therapy for psoriasis not achieving clearance after 4 weeks of continuous treatment. A total of 588 patients were initially screened and 303 were finally randomized. The impact of a dietetic plan associated with advice on physical exercise was compared with a simple informative counseling about the utility of weight loss during a 20-week period. The dietetic plan was based on the exchange system, in which foods are divided into groups, and, within each group, the maximum food allowance is defined based on the amount of calories involved. The main outcome was any reduction of PASI score from baseline at week 20. The target weight reduction was a loss equal to or greater than 5% of baseline weight at week 20. Outcome parameters were evaluated by an assessor, different from the treating physician, blind to the patient treatment allocation. Only 29 enrolled patients (6.9%) withdrew before the end of the study. Intention-to-treat analysis showed a median PASI score reduction of 48% in the dietary intervention arm and 25.5% in the information-only arm ( $P = .02$ ). The weight-loss target was reached by 29.8% of patients in the dietary intervention arm and 14.5% in the information-only arm ( $P = .001$ ). Interestingly, there was a clear correlation between the amount of weight loss and the improvement of psoriasis expressed as percent reduction of PASI

value, both in the intervention arm and in the information-only arm.

All in all, our study documented that, in the short term, even limited weight loss could help reduce psoriasis severity in overweight or obese patients, increasing the efficacy of systemic treatment. Interestingly, similar to metabolic control in diabetes,<sup>3</sup> we showed that even a small reduction in body weight may have a large clinical influence on disease activity.

The long-term impact of a dietetic intervention on psoriasis remains to be documented, and we are exploring the possibility of promoting a larger international collaboration focusing on the impact of dietetic interventions in the long-term management of psoriasis and its comorbidities, possibly by nesting randomized trials within existing disease registries.

Simone Cazzaniga, PhD,<sup>a</sup> Andrea Conti, MD,<sup>b</sup> Luigi Naldi, MD,<sup>a,c</sup> on behalf of the Psoriasis Emilia Romagna Study Group

Centro Studi Gruppo Italiano Studi Epidemiologici in Dermatologia (GISED), Bergamo, Italy<sup>a</sup>; Department of Dermatology, Azienda Ospedaliero-Universitaria-Policlinico, Modena, Italy<sup>b</sup>; and Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy<sup>c</sup>

Supported by a research grant from the Emilia Romagna region (Programma di Ricerca Regione Università 2007-2009, AREA 2 Ricerca per il governo clinico).

Conflicts of interest: None declared.

Correspondence to: Luigi Naldi, MD, Centro Studi GISED, Via Garibaldi 13/15, 24122 Bergamo, Italy

E-mail: [luigi.naldi@gised.it](mailto:luigi.naldi@gised.it)

### REFERENCES

1. Debbaneh M, Millsop JW, Bhatia BK, Koo J, Liao W. Diet and psoriasis, part I: impact of weight loss interventions. *J Am Acad Dermatol* 2014;71:133-40.
2. Naldi L, Conti A, Cazzaniga S, Patrizi A, Pazzaglia M, Lanzoni A, et al; the Psoriasis Emilia Romagna Study Group. Diet and physical exercise in psoriasis: a randomized controlled trial. *Br J Dermatol* 2014;170:634-42.
3. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001;414:782-7.

<http://dx.doi.org/10.1016/j.jaad.2014.05.072>

### The use of tumor necrosis factor inhibitors in pregnancy: What is the evidence?

*To the Editor:* We commend Murase et al<sup>1</sup> on their excellent review of the use of medications for dermatologic conditions in pregnant and lactating