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The diagnosis of melanoma

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"Despite the fact that the melanoma incidence increases annually, our diagnostic acumen remains significantly less than what we would like."

"The prime reason we are concerned about melanoma, and the justification behind new and expensive therapies, is that melanoma kills people; furthermore, the people it kills are often in the prime of life, younger than the typical patient who dies from cancer … We must cut the mortality rate by at least half, but progress toward that goal has been elusive. The key to achieving this goal is early detection, because prevention, if it is ever to be effective, takes a very long time, and curative therapy, despite recent progress, remains an unrealized hope for most patients who have recurrent disease." [1].

Despite the fact that the melanoma incidence increases annually, our diagnostic acumen remains significantly less than what we would like. Therefore, in this issue of *Expert Review of Dermatology*, we will cover clinical aspects of the melanoma diagnosis and assessment of disease stage. In this special focus issue of *Expert Review of Dermatology*, melanoma experts from around the world will review laboratory and imaging tests in the initial workup of patients with newly diagnosed melanoma. Sentinel lymph node biopsy, presently the most accurate method of regional node staging in patients with newly diagnosed melanoma, will be evaluated in depth. Emphasis will be placed on review of the current and developing role of biomarkers in melanoma and their role in the future diagnosis of melanoma. Various authors will discuss the role of biopsy, dermoscopy and assessment of individual risk. This issue, on The Diagnosis of Melanoma, will bring together key experts in the field to provide a thorough examination of diagnosing one of the most lethal cancers known to man.

The issue will open with four important editorials. First, Sondak and colleagues comment on the prognostic significance of lymph node metastasis in pediatric melanoma [2]. Then, Nguyen and colleagues from the University of Colorado (CO, USA) discuss their view of aldehyde dehydrogenase isozymes as potential markers of cancer stem cells in human melanoma [3]. Ferris *et al.* from the University of Hawaii (HI, USA) comment on whether testing for *BAP1* germline mutations could be a useful tool for early melanoma diagnosis [4] and Lian and Murphy from Brigham and Women's Hospital, Harvard Medical School (MA, USA) write on the diagnostic implications of loss of 5-hmC for melanoma [5].

The issue goes on to include an interview with Jeffrey S Weber from the H. Lee Moffitt Cancer Center (FL, USA) [6] and two evaluations of key papers in the field of melanoma diagnostics. These evaluations are contributed by Kovacic *et al.* [7] and Niebling *et al.* [8]. A meeting report by Dlova and Mosam is also included [9].

Moving on to the main body of the issue, Piérard and colleagues from the University Hospital of Liège (Liège, Belgium) will review the role of proteomics and immunohistochemistry in the differential diagnosis of melanoma from atypical melanocytic neoplasms [10]. The multiple acronyms for these lesions include atypical Spitz tumor, metastasizing Spitz tumor, borderline and intermediate melanocytic tumor, malignant Spitz nevus, pigmented epithelioid melanocytoma or animal-type melanoma,

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MELTUMP (melanocytic tumor of uncertain malignant potential) and STUMP (Spitzoid melanocytic tumor of uncertain malignant potential). Piérard *et al.* groups these atypical melanocytic neoplasm variants under the broad heading 'cutaneous melanocytoma'. These lesions usually have an indolent course despite the fact that they exhibit atypical patterns and cytology. Nonetheless, rare cases progress to locoregional clusters of lesions and to regional lymph nodes. The distinction between a cutaneous melanocytoma and melanoma remains problematic and occasionally proves to be impossible. Piérard *et al.* recommends multipronged immunohistochemistry to help assessing the malignancy risk of these lesions.

Argenziano and colleagues review problematic melanocytic lesions in children, specifically congenital melanocytic nevi and Spitz nevi, with special attention to the clinical and dermoscopic features of these lesions. The risk of melanoma in childhood and the risk of melanoma arising in congenital melanocytic nevi are discussed in depth [11].

Approximately, 50% of melanomas harbor an activating mutation in codon 600 of the *BRAF* gene and *KIT* mutations are found in 10–20% of acral melanomas, mucosal melanomas and melanomas on chronically sun-damaged skin. Takata *et al.* from Okayama University Graduate School of Medicine (Okayama, Japan) discusses identifying *BRAF* and *KIT* mutations in melanoma. The efficacy of oral kinase inhibitors, such as vemurafenib and imatinib, for melanomas harboring mutations in *BRAF* and *KIT* genes, have resulted in new standards of molecular testing to identify mutations in these oncogenes. Because of the intertumor heterogeneity of *BRAF* and *KIT* mutations, isolation and genotyping of circulating melanoma cells may provide vital information for optimal patient care [12].

Eggermont and colleagues then review the methodology and clinical utility of ultrasound-guided fine needle aspiration cytology of lymph nodes in melanoma patients. Early diagnosis of metastasis may lead to earlier surgical and systemic treatments and, therefore, may lead to an improvement of outcome in terms of relapse-free and overall survival [13].

Advances in infrared and computer technology in the past two decades have enabled the development of new, sophisticated medical imaging and diagnostic tools. For example, a quantitative infrared imaging system measures differences in the infrared emission between healthy tissue and lesional during the thermal recovery process after an applied cooling stress. Cila Herman from The Johns Hopkins University in Baltimore (MD, USA) reviews the role of an infrared skin cancer scanner in the diagnosis of melanoma [14]. New studies suggest that the temperature of cancerous lesions is higher during the first 45–60 s of thermal recovery than the temperature of benign pigmented lesions and this small temperature difference can be measured by modern infrared cameras. Therefore, this method holds the promise of becoming a quantitative diagnostic tool for skin cancer and a screening tool for early detection of melanoma.

Is the rising incidence of melanoma secondary to the concomitant explosion in indoor tanning? Qureshi and colleagues will review the evidence demonstrating that indoor tanning significantly increases an individual's risk of developing both melanoma and nonmelanoma skin cancers [15]. There is now evidence that indoor tanning may be the cause of the spike in melanoma incidence in women and young adults among whom tanning bed use and estimated risk ratios are higher than in the general population.

The proliferation of melanocytes within sun-damaged skin causes difficulties in histologically defining a malignant melanocytic lesion from the spectrum of actinic changes. Scolyer *et al.* discuss the controversies, challenges, and evolving concepts in the diagnosis, classification and management (both surgical and nonsurgical) of lentigo maligna [16]. Lentigo maligna usually has a long clinical course for evolution to invasive melanoma. Should we divide lentigo maligna into a premalignant/precursor (lentigo maligna) versus *in situ* melanoma (lentigo maligna *in situ* melanoma)? Since this neoplasm tends to spread laterally on cosmetically sensitive areas, when should definitive management be attempted? Since the tissue sample for histologic diagnosis is commonly a small proportion of the lesion and, because this neoplasm can show heterogeneous features in different parts of the lesions, how can we be sure that the representative tissue is diagnostic of the lesion? The answer to these questions plus the role of dermoscopy and *in vivo* confocal microscopy will be discussed regarding establishing the correct diagnosis and defining the margins of this neoplasm.

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