Pagetoid infiltration of the epidermis by melanocytes is a relevant criterion for the histologic diagnosis of melanoma, although sporadically observable in benign lesions. Since in vivo reflectance-mode confocal microscopy enables the visualization of superficial layers at cellular-level resolution, the different aspects and the diagnostic significance of epidermal alterations and pagetoid cell infiltration were investigated on 84 benign and malignant melanocytic lesions by confocal microscopy and compared with histopathology. The observation of a disarranged pattern in superficial layers appeared characteristic for malignant lesions. In vivo identification of pagetoid cells, clearly present in the majority of melanomas and in a few benign lesions, seemed useful for melanoma diagnosis. An excellent concordance between confocal microscopy and histopathology was achieved. Moreover, identification of some characteristic features by confocal microscopy, such as large and numerous closely arranged cells extended to the stratum corneum, was strongly correlated with malignancy. In conclusion, confocal microscopy enabled a very good identification of melanocytes spreading upward in a pagetoid fashion in melanocytic lesions. Thus, when pagetoid melanocytosis is observable by means of confocal microscopy, melanoma diagnosis should be considered, whereas it cannot be excluded in the absence of pagetoid cells, lacking in at least 10% of malignant lesions.