Animal-Type Melanoma – a Mini-Review Concerning One of the Rarest Variants of Human Melanoma

Melanom animálního typu – velmi vzácná varianta lidského melanomu

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Described for centuries in the equines, especially gray horses, as "equine melanotic disease", it was later recognized in non-equine animal models and in humans, particularly on non UV-exposed skin. Animal-type melanoma, also known as pigmented epithelioid melanocytoma (PEM), is characterized by nodules and fascicles of epithelioid transformed melanocytes with pleomorphic nuclei and striking pigmentation, dendritic cells, numerous melanophages and, sometimes, lymphocytic infiltrate [1,2]. Up-to-date, only small series have been reported in humans and, therefore, its biological behavior remains unclear [3]. In 2010, Ludgate et al. examined the clinical behavior of 8 cases of equivocal and 14 cases of unequivocal PEM, concluding that it shows a propensity for regional nodal metastases [4]. By systematic review and meta-analysis of the English literature, in 2015, Vyas et al. have identified 190 cases of PEM. The median Breslow depth was 3.8 mm, loco-regional recurrence was found in 15 cases, recurrence with distant metastases in 6 cases and death occurred in 5 patients [5]. Recently, Bax et al. have suggested that the tumor follows an indolent clinical course, with very low risk of spread beyond regional lymph nodes [6]. Given the complexity of the matter, Elder and Murphy proposed a histological categorization of PEM and PEM-like lesions, with distinctive clinicopathological and biologic attitudes [7]. In this review, we briefly highlight the current information about this rare disease.

Epithelioid blue nevus resembling PEM

It is a hyperpigmented, poorly circumscribed, dermal lesion, which shows heavily pigmented globular melanocytes, intermingled with hypopigmented spindle melanocytes. Commonly misinterpreted as classical blue nevus, in which markedly pigmented, bipolar, spindled cells are associated with a host-derived fibroblastic reaction, or as cellular blue nevus, a dermal-hypodermic benign neoplasm characterized by an alveolar or fascicular pattern of growth sometimes with neuronevoid aspects, or as PEM (see later); its exact identification is important because it is strongly associated with the Carney complex [8]. Conservative excision is generally recommended; moreover, affected patients (and their relatives) should be considered at risk for other diseases of the Carney complex, especially cardiac myxoma [8].

PEM

Not associated with the Carney complex, it is quite similar to epithelioid blue nevus at scanning magnification, but cytological atypia and sparse low mitogenicity are encountered by a careful histological inspection, exactly as observable in melanocytic tumors of uncertain malignant potential (MELTUMP) [9–11]. When epidermal pagetoid diffusion and overtly anaplastic nuclei are present, a diagnosis of

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malignant melanoma with prominent pigment synthesis can be also proposed [2]. Although the tumor can be lethal given the depth of invasion according to Magro et al., it seems to be less aggressive than other usual or unusual vertical growth phase melanomas [1,2]. Local lymph nodes are often involved by metastases – lymph node sentinel biopsy is recommended and a wide re-excision (1–2 cm margins) must be performed. Follow-up, as in any case of invasive malignant melanoma, should be conducted [2].

Tumoral melanosis mimicking PEM

It is a nodular cluster of melanophages, and it may represent a complete regression of a vertical growth phase melanoma or of a pigmented basal cell carcinoma [7]. In the radial and vertical growth phases, regression has negative impact on prognosis [12–16]; therefore, the follow-up should be very accurate since the lesion could be the result of a preceding, completely regressed melanoma [17–21].

A proper diagnostic framing is crucial in these controversial cases and a good histology in the hands of an expert dermatopathologist remains the most reliable diagnostic starting point. Moreover, a loss of expression of cAMP-dependent protein kinase type I-alpha regulatory subunit, an enzyme encoded by the tumor-suppressor gene *PRKAR1A*, has been found in PEM, but not in common melanoma or other melanocytic lesions [22]. Therefore, it appears to have a great diagnostic value in helping to distinguish PEM from PEM-like lesions, which mimic the former histologically.

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