If Cellular Blue Melanocytic Lesions Do Not Form a Spectrum...

To the Editor:

The interesting article entitled Cellular blue melanocytic lesions: analysis of clinical, histological, and outcome data in 37 cases, recently published in the American Journal of Dermatopathology, reported the clinicopathological features and the clinical course of a series of cellular blue melanocytic lesions (CBMLs). Hung et al analyzed 8 cellular blue nevi (CBNs), 17 atypical cellular blue nevi (ACBNs), and 12 blue nevus-like melanomas (BNLMs) (malignant blue nevi), performing molecular investigations (comparative genomic hybridization and polymerase chain reaction) in 3 ABCNs and in 1 BNLM. The authors concluded that “ACBN occupy an intermediate position within the spectrum of CBN and BNLM,” but many ACBNs “cannot be reliably distinguished from either CBN or BNLM because of overlapping histologic features” and of “lack of consensus for diagnosis...even among experts.” Summarizing, in this paper, as in other previous studies, mutatis mutandis, CBMLs seem to propose the same problems found in Spitzoid neoplasms, in which the distinction of atypical Spitz tumors from either Spitz nevus or Spitzoid melanoma is highly problematic and the diagnostic consensus is lacking.

In this context, an important question may be why the diagnosis of CBMLs (and, similarly, of Spitzoid neoplasms) is so difficult and the diagnostic concordance level so low. Many possible causes may be invoked. It has been stated that these problems may be due to failure of human brain; however, it is very difficult to understand why human brain does not generally fail in the diagnosis of basal cell carcinoma, solar keratosis or dermatofibroma, and so frequently fails in melanocytic lesions, including CBMLs.

Alternatively, a cause might reside in the histological criteria currently used to segregate benign from malignant forms; they could not work properly because they were not adequately studied. Actually, an examination of the pertinent literature shows that histological differential criteria between CBN and malignant blue nevus (MBN) have been very accurately studied. An additional possible cause, although not currently adequately considered, may be that CBMLs are regarded by a wrong or inadequate perspective (once again, similarly to Spitzoid neoplasms).

Interestingly, in a recent article, analyzing 22 atypical blue nevi and 35 atypical Spitz tumors, Cerroni et al have written: “the lack of clear-cut histopathologic differences between cases with favorable and those with unfavorable behavior suggests that these 2 groups may represent prognostic rather than diagnostic categories, and that these lesions may be considered as a group...of low-grade malignant melanocytic tumors.” In other words, according to Cerroni et al, ACBNs would not be “biologically indeterminate” neoplasms, as Hung et al believe, but low-grade melanomas (different from “conventional melanomas”). The notion that ACBNs properly are low-grade melanomas may explain many, if not all, current problems, including why ACBNs are so similar to MBN, why they are not confidently separable by any special technique, why more than occasionally the attempts to differentiate them fail, and finally why the diagnostic concordance of pathologists is so low. The notion of ACBN as a neoplasm with low malignant potential might also explain why occasionally cellular deposits may be found in sentinel and nonsentinel nodes and why, notwithstanding this, the clinical course of many patients is not unfavorable.

Moreover, extending our analysis from ACBN to the entire category of CBMLs, it is interesting to carefully scrutinize Table 2, published by Hung et al, concerning the differential features between CBN, ACBN, and MBN. In this table, no one single criterion or groups of criteria seemed to be really distinctive of ACBN in respect to MBN. All parameters listed were shared by both the neoplasms. There is no substantial difference in their histological appearances or in their structures but only a modulation of the histological features, being less pronounced in ACBN and more prominent in MBN. ACBN and MBN seem to have the same histological characteristics; morphologically and structurally, they appear as being a unique tumor. In addition, in the same table, the same circumstances can be noted comparing ACBN to MBN. Again, no one single criterion or groups of criteria seem to be distinctive of ACBN in respect to CBN—with the exception of the parameter “infiltrative borders,” that, however, may not be observed in some ACBNs and, conversely, is said “generally” absent (ie, sometimes present) in CBNs. All parameters listed were shared by both the neoplasms. There is no substantial difference in their histological appearances or in their structures but only a modulation of the histological features, being less pronounced in CBN and more prominent in ACBN. ACBN and CBN seem to have the same histological characteristics; morphologically and structurally, they appear as being a unique tumor. In sum, CBMLs do not appear as 3 different tumors, nor as forming a spectrum of lesions, confidently distinguishable and clearly diagnosable. All CBMLs, including forms currently labeled as CBN, ACBN, and MBN, share the same histological characteristics and, morphologically and structurally, appear as being a unique entity, that shows a modulation of the histological features, of the risk and, consequently, of the prognosis.

This unique entity, which may be termed as cellular blue tumor (CBT), appears as a dermal tumor, histologically characterized by the presence of “oval to plump spindle cells intermingled with dendritic melanocytic cells and variable numbers of melanophages.” CBT is not benign, not indeterminate, not borderline, not ambiguous, and not enigmatic. It is malignant, but seems to possess a low malignant potential, globally lower than that observed in a conventional melanoma of the same thickness. A tumor with low malignant potential is not necessarily a tumor having an invariably limited metastatic capability (eg, a tumor capable of regional but not distant metastatic spread).
metastases). It can be a tumor with a metastatic rate statistically lower than expected. However, the malignant potential of CBT is variable, because it is not same in all the cases. Currently, it is not possible to obtain a precise quantitative estimation of the malignant potential of a single tumor, but it is possible to approximately estimate it, evaluating the amount of the potential risk. In CBT, this risk may range from very low to high and may be expressible as statistical probability that an adverse event (local, nodal or visceral metastases) will occur; or is detected; however, in each single case, the prognosis is unpredictable, being a matter of probability. For an evaluation of the potential risk of a CBT, features associated with adverse events may be considered. In 2008, a list of histological features associated with metastases and/or a potentially adverse prognosis was compiled. A revised list may include the following 9 histological parameters: (1) dimension ≥1 cm, (2) marked asymmetry, (3) infiltrative borders, (4) cellular heterogeneity and/or cytologic atypia, (5) epidermal involvement or ulceration, (6) mitoses (≥2 per section), (7) atypical mitoses, (8) necrosis, (9) inflammatory infiltrate. It is suggested that the very presence of at least one of the parameters of this list is to be considered as a sufficient condition for a diagnosis of potential malignancy and should discourage a diagnosis of a benign lesion. Lesions showing one or more of the parameters 6–9 have been shown to be relatively frequently associated with adverse events6,7,9,10 and should be considered “cellular blue tumors with high risk” (CBT3). Lesions showing one or more of the parameters 1–5 have been shown to be less frequently or rarely associated with adverse events6,7,9,10 and should be considered “cellular blue tumors with low or moderate risk” (CBT2). Lesions showing none of parameters 1–9 (therefore, small <1 cm, symmetric, with uniform/nontypical cells and pushing borders, without necrosis, mitoses, ulceration, or inflammatory infiltrate) have been shown to be very rarely associated with adverse events6,7,9,10 and should be considered “cellular blue tumors with very low risk” (CBT1). In this schema, most lesions currently diagnosable as CBMs are included into CBT1, because, in these lesions, it is objectively impossible to exclude an implicit minimal risk. In fact, lesions labeled as CBMs, classified as benign nevi, without adequate experimental data, by Allen in 1949,13 have been subsequently sporadically reported to show a possible locally aggressive behavior with infiltrative growth, cutaneous satellite lesions, subcutaneous nodules, and lymph node deposits, although, usually (but not invariably) with a good prognosis.14–21 Results of genomic analysis may be used for a further evaluation of risk. Provisionally, fluorescence in situ hybridization analysis (targeting RREB1, MYB, CCND1, and Cep6), if positive, should prevent the diagnosis of CBT22; if negative, it should not impede the diagnoses of CBT2 and CBT3. Moreover, analyzing a series of lesions with comparative genomic hybridization (10 cases diagnosed as CBMs, 8 cases labeled as ACBMs, and 7 cases diagnosed as MBNs or melanomas mimicking a blue nevus), Maize et al23 have found that the presence of at least 3 chromosomal aberrations (the most common, loss of chromosome 9, and gain of chromosome 20) is suggestive for a malignant behavior; therefore, the presence of 3 or more chromosomal aberrations, indicating a high risk, should prevent the diagnoses of CBT1 and CBT2.

In conclusion, if CBMLs do not form a spectrum, but represent a unique tumor (CBT), diagnostic problems tend to vanish: the diagnosis becomes not only possible, but relatively easy, relying only on the recognition of the peculiar cell types constituting the lesion; the concordance level may be higher, because parameters are less numerous and evaluated as in a binary fashion (present/absent). On the basis of the classes of risk (CBT1, CBT2, and CBT3), an appropriate gradable management of patients with CBT can be established.

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REFERENCES


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