Title: Trichoepitelioma and trichoblastoma: the role of dermoscopy in differentiating benign follicular tumors from basal cells carcinoma

Background: Adnexal skin tumors represent a wide spectrum of tumors showing differentiation toward follicular, sebaceous, eccrine or apocrine glands structures.[1] On clinical and dermoscopic examination many adnexal tumors may mimic other benign and malignant skin cancers. Among these, benign follicular tumors, in particular trichoepithelioma, its desmoplastic variant and trichoblastoma, have been shown to be basal cells carcinoma (BCC) mimickers. Indeed, no specific clinical and dermoscopic criteria have been described for these tumors allowing to differentiate them from BCC.[2,3] However, no studies have been conducted on large series of benign follicular tumors, in which cases were compared with a control group of BCCs and evaluated by blinded experts. The aim of our study is to evaluate if some clinical and dermoscopic criteria may allow to differentiate between benign follicular skin tumors and BCC. When available, also the role of in-vivo reflectance confocal microscopy will be considered. We also aim to describe the dermoscopic features of these benign tumors in a large population of patients. We retain that the identification of specific criteria for benign follicular tumors diagnosis would be able to reduce the number of unnecessary biopsies and excisions.

Methods: this case-control retrospective study will consist of 2 phases. In the first phase a database of clinical and dermoscopic pictures of histopathologically confirmed benign follicular tumors (cases) and BCCs (controls) will be constructed. Only completely excised tumors will be included. Members of the International Dermoscopy Society will be asked to contribute to this part of the study. Our purpose is to collect at least 50 cases for each of the following benign follicular tumors: trichoepitelioma, desmoplastic trichoepitelioma and trichoblastoma. A double number of histopathologically confirmed BCC cases will be included in the control group. Controls will be randomly selected from the database of the Skin Cancer Unit – Centro Oncologico ad Alta Tecnologia

Diagnostica of Reggio Emilia and will be matched with cases according to the anatomic location and palpability (flat vs. palpable lesions); also, superficial BCCs will be excluded.

Patients will consent for photography at their respective centers and data will be de-identified. In addition, to prevent patient identification, only close-up clinical pictures will be provided, together with dermoscopic and confocal images. Only high-quality clinical and dermoscopic images will be included. Demographic and clinical information will be also provided anonymously (sex, age, histopathological diagnosis and histological subtype, body site, palpability (flat vs. palpable) and clinical diameter if not indicated in the picture). The polarized contactless dermoscopic technique will be preferred; however, non-polarized pictures will be also accepted and images taken by contact dermoscopy will be included only if taken with the use of gel. In the second phase the clinical, dermoscopic and confocal images will be evaluated in the reported order by 2 physicians with experience in dermoscopy and confocal microscopy for the presence of specific criteria. A specific diagnosis will be indicated by each evaluator based on the clinical aspect alone, clinical + dermoscopic and clinical + dermoscopic + confocal evaluations. In case of disagreement, a third experiences physician will be asked to solve the issue. All the evaluators will be blind for the final diagnosis. No specific lists of criteria will be given to evaluators. A final list of criteria will be redacted by the three evaluators in consensus, after the evaluation process. Since we expect that confocal images will be only available for a minority of the enrolled cases, confocal assessment will be considered as an exploratory endpoint.

Sample size calculation: We are planning a study of independent cases and controls with 2 controls per case. Prior data indicate that the majority of clinical and dermoscopic criteria only minimally differ from case and controls. If we assume a difference of 15% between cases and control for a given clinical or dermoscopic criterion, we will need to study almost 150 cases and 300 controls to be able to reject the null hypothesis that the distribution of that criterion is equal between cases and controls,

with probability (power) of 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis. We've also planned to test our results on an external test set that will be created by enrolling 45 more cases (15 trichoepiteliomas, 15 desmoplastic trichoepiteliomas and 15 trichoblastomas) and 90 more controls. These lesions will be randomly selected from case and control groups, respectively; thus, the final sample size will include a total of 195 lesions for cases and 390 for controls.

Institutional review board (IRB) approval

IRB approval will be obtained by the central academic institution. Since data from the other involved centers will be provided anonymously and only close-up and dermoscopic pictures will be requested with no identifiable features, IRB approval will be waived for these study sites.

Statistical analysis: Statistical analyses will be performed using the IBM SPSS 22.0 package (Statistical Package for Social Sciences, SPSS Inc., Chicago, Ill.). Absolute and relative frequencies for clinical characteristics, dermoscopic and confocal criteria will be calculated. Sensitivity, specificity, positive and negative predictive values in differentiating benign follicular skin tumors from BCCs will be calculated for clinical diagnosis alone, clinical + dermoscopic and clinical + dermoscopic + confocal diagnosis. Receiver operating characteristic (ROC) curves will be constructed and Area under the Curves (AUC) calculated. Uncorrected chi-square test will be used for qualitative and Student T test for quantitative variables.

To analyse clinical and dermoscopic factors independently associated with benign follicular tumor diagnosis, we will use Spearman's rho coefficient to flag significant correlations, which were subsequently quantified via univariate logistic regression. Furthermore, a logistic multivariate regression model with backward stepwise variable selection will constructed to identify major independent factors among the descriptors that showed a significant difference ($p<0.10$) on univariate analysis, together with the notable intervariable interactions. If possible, a score will be constructed

for differentiating cases from controls. Sensitivity, specificity, negative and positive predicting values will be calculated for this score, together with the ROC curve and the AUC value. Alpha level will be set at 0.05. Since confocal pictures will be provided only if available, differences among groups according to the distribution of specific confocal criteria will be only considered in the univariate analysis and not included either in the multivariate model or in the score.

Expected results: Considering the sample size we have planned to enroll in this study, a difference of at least 10% for a given clinical or dermoscopic criterion among the groups will permit to identify a statistically significant difference. We do expect to find more than 1 criterion significantly associated with the group of cases or controls. This finding will allow to create a diagnostic score.

References

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