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Multiple primary melanomas: Is there a correlation between dermoscopic features and germline mutations?

Several studies have shown that cutaneous melanoma (CM) patients have an increased risk of developing multiple primary CMs (MPMs) in 1.3%–8.0% of the cases, up to 12% in familial settings. Subsequent CMs are more likely to be identified within 2 years from the first diagnosis, usually showing a lower Breslow thickness, probably due to an increased surveillance.[1,2] MPMs can be synchronous, when diagnosed within 3 months after the previous diagnosis or metachronous in case of a later detection; subsequent CMs often occur on the same site of the initial one.[2,3] Germline mutations in the high-penetrance CM susceptibility gene *CDKN2A* (*cyclin-dependent kinase inhibitor 2A*) have been found in 5%–40% of subjects with familial CMs and in 8%–15% of those with MPMs without familial history; *CDK4* (*cyclin-dependent kinase 4*), *MITF* (*microphtalmia-associated transcription factor*) *TERT, TYRP1, MTAP, TYR* and *MX2* are more rarely mutated.[2,4]

We conducted a retrospective, monocentric analysis of MPMs patients diagnosed at IRCCS Azienda Ospedaliero Universitaria di Bologna between January 2005 and December 2021 with the availability of the germinal genetic status. Extracutaneous CMs, unknown primary CMs and patients with missing data were excluded. Patient's consent form was obtained. Dermoscopic images

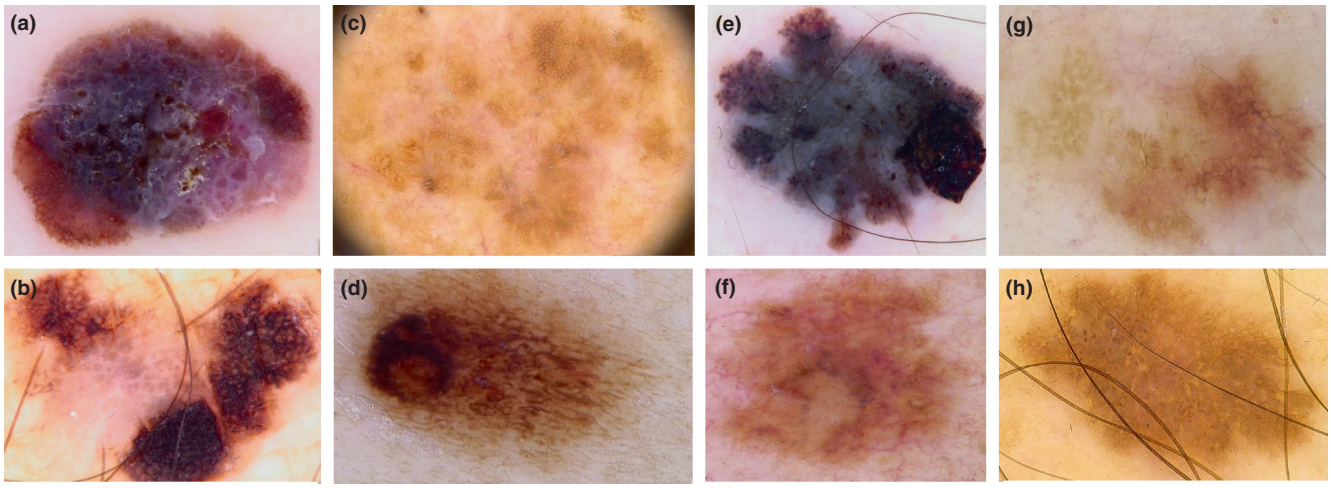

FIGURE 1 Dermoscopic presentation of selected MPMs cases in our series: (a, b) dermoscopic concordance of synchronous MPMs (6/8 analogue criteria: atypical network, regression structures, structureless areas, irregular vessels, inverse network, blue-white veil); (c, d) dermoscopic discordance of synchronous MPMs (2/8 analogue criteria: atypical network, structureless areas); (e, f) dermoscopic discordance of synchronous MPMs (3/8 analogue criteria: atypical network, regression structures, structureless areas); (g, h) dermoscopic concordance of synchronous MPMs (4/8 analogue criteria: atypical network, regression structures, structureless areas, inverse network).

TABLE 1 Clinical, mutational status, histopathologic, and dermoscopic data of patients included in the study.

Total of patients (*n*)/total melanomas (*n*)	106/254
Sex (*n*, %):	
M	65 (61.3%)
F	41 (38.7%)
M:F	1.6
Mean age at first diagnosis (years)	58.6
Familial history (*n*, %):	
Negative	90 (84.9%)
Positive	16 (15.1%)
Localization of first CM (*n*, %):	
Trunk	73 (68.9%)
Limbs	23 (21.7%)
Head/neck	6 (5.7%)
Acral sites	4 (3.7%)
Total of MPMs developed (*n*, %):	
Two	76 (71.7%)
Three	22 (20.8%)
Four	5 (4.7%)
Five	2 (1.9%)
Six	1 (0.9%)
Synchronicity of at least one MPM	25 (23.6%)
Site agreement of at least one MPM	35 (33.0%)
Mean time after recurrences (years)	1.8
Breslow thickness of first CM:	
Mean (mm)	1.03
In situ (*n*, %)	9 (8.5%)
Breslow thickness of subsequent MPM:	
Mean (mm)	0.55
In situ (*n*, %)	27 (18.3%) $p = 0.6636$
Histopathologic subtype of first MM (*n*, %):	
Superficial spreading	92 (86.7%)
Lentigo Maligna	10 (9.4%)
Acral	4 (3.8%)
Histopathologic subtype of subsequent MPMs (*n*, %): (total of subsequent MPMs 148)	
Superficial spreading	132 (89.2%)
Lentigo Maligna	14 (9.5%)
Acral	2 (1.4%)
Concordance of histopathologic subtype between first CM and subsequent MPMs (*n*, %)	(total of subsequent MPMs 148) 127 (85.8%)
Dermoscopic criteria:	
Atypical network	184 (72.44%)
Regression structures	150 (59.05%)
Structureless areas	96 (37.80%)
Irregular vessels	54 (21.26%)
Inverse network	40 (15.74%)
Blue-white veil	40 (15.74%)
Irregular dots	36 (14.17%)
Globules and streaks	32 (12.59%)
Concordance of dermoscopic criteria between first CM and subsequent MPMs (*n*, %):	59 (55.7%)
M	36 (61.5%)
F	23 (38.5%) $p = 0.4066$
CDKN2A mutation/polymorphism (*n*,%)	Prevalent dermoscopic pattern (*n*,%)
c.442G>A (p.Ala148Thr)[a]; 6 (5.66%)	Atypical network (5/6, 83.3)
c.249C>A, p.His83Gln[b]; 3 (2.80%)	Atypical network (2/3, 66,6%)
MITF mutation (*n*, %)	
c.952G>A p.Glu318Lys; 3 (2.80%)	Structureless areas (3/3, 100%) Irregular vessels (3/3, 100%)

Notes: http://oncokb.org/#/; https://ckb.jax.org; https://www.ncbi.nlm.nih.gov/clinvar/; http://genetics.bwh.harvard.edu/pph2/; https://gnomad.broadinstitute.org/; https://databases.lovd.nl/shared/genes/CDKN2A.

[a]OncoKB (Inconclusive); CKB (No protein effect); Clinvar (benign); Polyphen (Benign-Score 0.07 HumVar) gnomAD (benign); Leiden database (benign, likely benign or VUS).

[b]OncoKB (Likely Oncogenic); CKB (Unknown protein effect); Clinvar (Likely pathogenic); Polyphen (score 1 -Probably damaging (HumVar)); Leiden database (VUS).

were evaluated in random order by 4 expert dermatologists (G.V., M.M., F.T., E.D.). The following dermoscopic criteria were assessed: regression structures, atypical network, structureless areas, irregular vessels, inverse network and blue-white veil, irregular dots/globules and streaks. Each dermatologist compared the images of every single patient to detect any criteria concordance, defined as the presence of at least 4/8 analogue criteria in both CMs (Figure 1). Data regarding germline mutations in *CDKN2A, CDKN2B, CDK4* and *MITF* genes were evaluated: overall, 106 patients were included, 65 males and 41 females, with a total of 254 CMs (Table 1).

Statistical analysis did not show any significant association between concordance of dermoscopic criteria and sex, synchronicity of MPMs and anatomical site.

Currently, a possible association between germline mutations and dermoscopic features has been proposed.[5,6] Structureless areas are often detected in case of *CDKN2A* mutations with a couple of variants of *MC1R* of the RHC type and streaks/pigmented networks in their absence.

MITF-mutated subjects may show a nonspecific pattern (amelanotic/hypomelanotic nodular CM) with atypical polymorphic vessels.[6,7] *RHC MC1R* variants were reported to influence CM features, reducing the pigmentation and the development of dermoscopic structures, including a lower number of blotches, due to the reduced synthesis of eumelanin. Non-carriers of *RHC* variants were shown to have darker shades of colours, asymmetry and more structures.[6] Specific genetic variants in *MTAP* (allele rs10811629_G, rs2218220_T and rs7023329_G) were correlated with regression structures (peppering, mixed regression), blue-whitish veil, shiny white structures and pigment network, while others in *PAX3* (allele rs132985_T), *PLA2G6* (rs7600206_C), *IRF4* (rs12203592_T) with shiny white structures or mixed regression.[6]

In our series, structureless areas and irregular vessels (both 3/3, 100%) were the most common patterns in *MITF*-mutated patients compared to 37.80% and 21.26% in the whole group ($p = 0.045$ and 0.008, respectively), while the atypical network was the most common pattern in *CDKN2A*-mutated cases or in those with polymorphism, though the difference was not statistically significative (5/6 in c.442G>A and 2/3 in c.249C>A; $p = 0.482$ and 0.614, respectively). Moreover, 2/3 *MITF*-mutated patients developed a nodular amelanotic CM after a pT1a cM during the longitudinal follow-up.

We detected no correlation between the germline mutational status and the MPM concordance, even considering the low rate of mutated cases.

Moscarella et al. reported a concordance rate respectively in 53.0% and 38.7% of MPMs.[8] Colombino et al. reported a higher concordance rate (66.7%) but limited to only 12 patients. In our study, the concordance rate was 55.7%, consistently with previous studies.[9] This was higher in males (61.5%) than in females (38.5%). One of the main aims of CM follow-up programs is to ensure a prompt detection and excision of atypical lesions. CM subjects may show a considerable number of nevi, often in a multiple dysplastic nevus syndrome. Considering that more than half of MPMs patients show a concordance between dermoscopic patterns, we believe that knowing the dermoscopic features of the first diagnosed CM may help the clinicians in the evaluation and decisional process of doubtful lesions. Though the germline mutational status does not appear to be correlated with a concordance in MPM dermoscopic presentation, but further studies are warranted.

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KEYWORDS

dermato-oncology, dermatopathology, dermoscopy, germline mutations, genetic, melanoma

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CONFLICT OF INTEREST STATEMENT

None.

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Evaluation of teledermatology during a pandemic: Assessing patient satisfaction, cost evaluation and clinical effectiveness

In this report, we evaluate teledermatology during a pandemic by assessing clinical effectiveness, cost, quality of life and patient satisfaction in an Australian context.

This single-centre cross-sectional study of teledermatology was conducted at an Australian tertiary hospital using a three-part questionnaire—dermatology life quality index (DLQI), patient satisfaction questionnaire (PSQ) and cost evaluation questionnaire—between 17 February and 24 December 2020, after HREC approval (*Melbourne Health HREC/61778/MH-2020*). From the group of teledermatology patients, patients with psoriasis on biologic therapy were analysed as a sub-cohort. The primary outcome was patient satisfaction. The secondary outcomes were clinical effectiveness, cost and waiting time for appointments and waiting time in waiting area.

The DLQI score was calculated by summing the score of each question (0–30). The scores were divided into two categories—'moderate to large effect' (6–30) and 'no to mild effect' (0–5).

The 12-item PSQ (adapted from a validated 15-item questionnaire) evaluates patient satisfaction.[1] The response scale was divided into 'disagree', 'no opinion' and 'agree'. Negatively worded satisfaction items were recorded in reverse, so that a higher score reflects greater satisfaction. The PSQ was divided into four categories: positive attitude, hotel aspects, photo anxiety and interaction.[1] The Spearman rank-order correlation coefficient was used to measure the association between DLQI and PSQ.

A cost evaluation questionnaire was created to evaluate costs saved attending teledermatology appointments and analysed using descriptive statistics.

Clinical effectiveness was evaluated by comparing PASI and DLQI in patients on ongoing biologic therapy

TABLE 1 Demographic and clinical characteristics of patients ($N = 191$).

	Frequency (%)
Age (years), (mean (SD))	54.5 (15.6)
Gender	
Male	95 (50%)
Female	91 (48%)
Missing	5 (3%)
Language spoken at home	
English	109 (57%)
Other	8 (4%)
Missing	74 (39%)
Highest level of education	
Secondary school or less	33 (17%)
Trade or other certificate level qualification	32 (17%)
Bachelor degree	28 (15%)
Postgraduate qualification	23 (12%)
Missing	75 (40%)
Geographical classification[a]	
Metropolitan	139 (73%)
Rural/Remote	52 (27%)
Type of skin conditions	
Papulosquamous/psoriasiform	85 (45%)
Eczematous	25 (13%)
Sebaceous and apocrine gland disorders	11 (6%)
Others	70 (36%)
Skin examination for skin malignancies	12 (6%)
Biologic therapy	71 (37%)
Teledermatology visit type	
Video	166 (87%)
Phone	25 (13%)

[a]Rural, Remote and Metropolitan Area (RRMA) classification.