Clinically amelanotic or hypomelanotic melanoma: Anatomic distribution, risk factors, and survival

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Background: The recognition and diagnosis of clinically amelanotic or hypomelanotic melanoma is a challenge.

Objective: This study aimed to examine the anatomic distribution and risk factors associated with clinically amelanotic or hypomelanotic melanoma and compare the survival of patients with clinically amelanotic or hypomelanotic melanoma with that of patients with pigmented melanoma.

Methods: A prospective cohort study of all cases of primary invasive melanoma managed at a tertiary referral center was performed.

Results: There were a total of 3913 invasive melanomas, and 384 (9.8%) were clinically amelanotic or hypomelanotic. Skin phototype I; red as well as blonde hair color; actinic keratoses; nodular, desmoplastic, and lentigo maligna subtype; increased Breslow thickness; and mitoses were independently associated with amelanotic or hypomelanotic melanoma ($P < .05$). After adjustment for subtype and thickness, the face, ears, lateral aspect of the neck, upper portion of the arm, posterior aspect of the forearm, dorsal aspect of the hand, and anterior aspect of the lower portion of the leg were associated with increased odds of amelanotic or hypomelanotic melanoma when compared with the upper portion of the back ($P < .05$). Mortality risk from melanoma appeared greater for amelanotic or hypomelanotic melanoma than for pigmented melanoma (hazard ratio, 1.5; 95% confidence interval, 1.1-2.1) but was similar once Breslow thickness was taken into account.

Limitations: Single tertiary referral center.

Conclusion: Although clinically amelanotic or hypomelanotic melanoma can occur on all body sites, it is more common on chronically sun-exposed areas. Clinicians should have an increased index of suspicion in patients with a sun-sensitive skin phenotype, red hair, and associated actinic keratoses. (J Am Acad Dermatol 2018;79:645-51.)

Key words: amelanotic melanoma; anatomic location; hypomelanotic melanoma; pigmentation; survival.

The recognition and diagnosis of clinically amelanotic or hypomelanotic melanoma may be the single greatest challenge for clinical diagnosis in further reducing deaths from melanoma.[1-4] With a lack of pigment on visual inspection, these melanomas cannot be detected by using color criteria under the conventional ABCDE (asymmetric shape, border, color, diameter, evolution) algorithm,[5] and they are often clinically misdiagnosed initially.[1-3] The importance of improving

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the detection of amelanotic or hypomelanotic melanoma is underscored by its association with adverse survival due to a more advanced stage at diagnosis.[6,7]

Amelanotic melanoma has been described in all histologic subtypes.[3,6,7] Previous studies using either clinical or histopathologic definitions for amelanosis have reported that amelanotic or hypomelanotic melanoma represents 2% to 20% of all melanomas.[3,6,8,9] Amelanotic or hypomelanotic melanoma is thought to grow more rapidly than pigmented melanoma[6,10,11] and to be associated with older age,[3,6,7] freckling,[12] and a sun-sensitive phenotype[12]. However, the relationship between sex and amelanotic or hypomelanotic melanoma remains uncertain.[3,6,7,13] A number of patients with amelanotic or hypomelanotic melanoma have been reported to carry the melanocortin 1 receptor gene (*MC1R*) genotypes linked to red hair color.[14,15]

CAPSULE SUMMARY

- Clinically amelanotic or hypomelanotic melanoma has a worse prognosis than pigmented melanoma, likely because of a delay in diagnosis.
- Although these melanomas occur on all body sites, they are more common on chronically sun-exposed areas.
- Clinicians should have an increased index of suspicion in patients with a sun-sensitive skin phenotype, red hair, and associated actinic keratoses.

Significantly, the anatomic distribution of amelanotic or hypomelanotic melanoma has not been examined in detail. Previous studies on amelanotic or hypomelanotic melanoma have used imprecise methods to describe anatomic site, typically dividing the body into large areas such as the head and neck, trunk, arms, and legs.[6,7] Furthermore, although pigment can usually be detected histopathologically in clinically amelanotic or hypomelanotic melanoma,[1] the difficulty in diagnosing amelanotic or hypomelanotic melanoma lies with the clinician and not the pathologist.[16]

The aims of our study were to examine in detail the anatomic distribution of clinically amelanotic or hypomelanotic melanoma, investigate the phenotypic factors associated with clinically amelanotic or hypomelanotic melanoma, and compare the survival outcomes of patients with clinically amelanotic or hypomelanotic melanoma with those of patients with pigmented melanoma.

METHODS

The Victorian Melanoma Service (VMS) is a statewide, multidisciplinary tertiary referral service based at the Alfred Hospital in Melbourne; it reviews approximately one-quarter of new melanoma cases in Victoria. The VMS research database is prospectively maintained and includes all patients treated at the service. All patients with primary invasive melanoma treated at the VMS during the period from 1994 to 2016 were included in this study.

Clinical features assessed and recorded in the database by the treating physician include age, sex, date of diagnosis, tumor location, amelanosis or hypomelanosis, Fitzpatrick skin type, hair color, actinic keratoses, and history of nonmelanoma skin cancer. Clinically amelanotic or hypomelanotic tumors were defined as those that appeared to the treating doctor or patient to be without pigmentation on visual inspection. Tumor location was recorded by using detailed coding across 232 anatomic sites based on a system developed by the Pigmented Lesion Study Group.[17] The histologic features assessed included tumor subtype, Breslow thickness, ulceration, and mitotic rate. Tumor subtype was classified according to World Health Organization guidelines as superficial spreading, lentigo maligna, acral lentiginous, nodular, or desmoplastic melanoma. Unclassified and rare subtypes such as spitzoid and nevoid melanoma were grouped as other. Patients were excluded from our study if information on tumor location, subtype, and thickness was not recorded. Mucosal, genital, and ocular melanomas were excluded.

Survival information for patients in the study was obtained by linkage with the Victorian Cancer Registry, which is a population-based cancer registry that collects data on all cancer diagnoses and mortality for residents in the state of Victoria, Australia. Patient vital status was current as of December 2015, and if applicable, date and cause of death were obtained. Only patients in whom invasive melanoma was diagnosed between 2002 and 2015 were included in survival analyses due to a lack of accurate registry information on cause of death before 2002. For patients with multiple primary melanomas, the pathologic characteristics of the tumor with the greatest Breslow thickness was used in the analyses.[18]

For statistical analysis, tumor location was first categorized broadly into 4 groups (head and neck, trunk, upper limb, and lower limb). For more detailed analyses of anatomic distribution, tumor location was categorized into 50 groups (Fig 1 and Supplemental Table I [available at http://www.jaad.org]). Age