7 Melanoma of Unknown Primary

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Abstract: Although the vast majority of melanomas have a known primary site, approximately 3.2% of all melanomas present in distant sites with no known primary site. Melanoma of unknown primary most often presents in lymph nodes, followed by subcutaneous sites, and finally visceral organs. Various hypotheses regarding the origin of melanoma of unknown primary have been proposed, including spontaneous regression of the primary tumor, and the presence of ectopic melanocytes within lymph nodes and visceral organs. Melanoma of unknown primary is less well studied in comparison with melanoma of known primary, but its clinical, molecular, and genetic characteristics have been recently clarified. Specifically, melanoma of unknown primary occurs more often in men in the fourth and fifth decades of life, and shares a similar genetic and molecular signature as cutaneous melanomas arising on skin that is intermittently exposed to the sun, including the back and upper legs. In addition, the prognosis of these patients has also been clarified, and patients with melanoma of unknown primary have improved survival compared to stage-matched patients with melanoma of known primary. This chapter reviews recent advances in the understanding of melanoma of unknown primary, highlighting its genetic and molecular characteristics, epidemiology, prognosis, and treatment, as well as its relationship with melanoma of known primary site.

Key words: Epidemiology; Melanoma of known primary; Melanoma of unknown primary; Metastatic melanoma; Prognosis

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INTRODUCTION

More than 97% of all melanomas are diagnosed with a known primary site, most often involving the skin (1). Less commonly, melanoma can present within the eye or mucous membranes (1). Rarely, melanoma is diagnosed without an obvious primary site, and is referred to as melanoma of unknown primary (MUP). In 1963, Das Gupta originally defined MUP as melanoma discovered in subcutaneous tissue, lymph nodes (LNs), or visceral organs without a cutaneous, ocular, or mucosal primary site (2).

Melanoma of known primary (MKP) is commonly misclassified as MUP. This error stems from a lack of knowledge regarding the melanoma's true primary site, which may result from an incomplete physical examination of all cutaneous, ocular, and mucosal surfaces, or from the history omitting a previously treated or regressed melanoma. Given the inherently problematic nature of accurately defining MUP in clinical practice, Das Gupta also described four exclusion criteria that were intended to aid in the characterization of MUP (Table 1) (2). If any of these exclusion criteria were met, Das Gupta proposed that patients be classified as having MKP rather than MUP (2).

Despite these proposed exclusion criteria, MUP patients described in the literature to date have been heterogeneous, with wide variations in how MUP is

TABLE 1 **Exclusion criteria for melanoma of unknown primary, originally proposed by Das Gupta (2)**

1. Evidence of previous orbital exenteration or enucleation
2. Evidence of previous skin excision, electrodessication, cauterization, or other surgical manipulation of a mole, freckle, birthmark, paronychia, or skin blemish
3. Evidence of metastatic melanoma in a draining lymph node with a scar in the area of skin supplying that lymph node basin
4. Lack of a nonthorough physical examination, including the absence of an ophthalmologic, anal, and genital exam

TABLE 2 **Common mutations in melanoma of unknown primary compared to melanoma of known primary**

Melanoma of unknown primary	*Melanoma of known primary*				
	Chronically sun-damaged skin	Intermittently sun-damaged skin	Acral	Mucosal	Ocular
BRAF > NRAS No c-KIT	c-KIT > NRAS > BRAF	BRAF > NRAS No c-KIT	c-KIT > BRAF > NRAS	c-KIT	GNAQ

defined, and in the interpretation of the exclusion criteria. In fact, in a recent systematic review of MUP, Kamposioras et al. reported that only 16% of peer-reviewed articles and abstracts used the original Das Gupta criteria for the characterization of MUP (3). Most commonly, studies vary in the comprehensiveness of the physical examination that is required before formally diagnosing MUP, including varying degrees of cutaneous, oral, ocular, otolaryngologic, urogenital, and proctoscopic evaluation (3). Particularly for mucosal surfaces, there is no consensus on how thorough an examination of mucosal sites must be before establishing a diagnosis of MUP (3).

HYPOTHESES REGARDING THE ORIGIN OF MUP

Since its original definition, various hypotheses have been put forth to help explain the biological phenomenon of MUP. Metastatic melanoma could theoretically develop synchronously with a subclinical or otherwise unrecognized cutaneous, ocular, or mucosal melanoma (2, 4). This is a less likely explanation for MUP if follow-up times are adequate, however, because the known primary will likely declare itself by the time metastatic disease has developed.

The predominant hypothesis for MUP involves the spontaneous regression of melanoma from a known primary site. The regression theory, first proposed by Smith and Stehlin in 1965, attributes the disappearance of a primary melanoma to spontaneous regression after metastasis has occurred (5). The partial or complete spontaneous regression of melanoma from a known primary site is well documented in the literature, and melanoma accounts for 11% of all cases of spontaneous tumor regression (6–9). However, whereas the partial regression of primary melanoma is fairly common, and is estimated to occur in 9–46% of all melanomas, complete regression is very rare, estimated to occur in only 0.22–0.27% of all melanomas (6, 10–13). Studies reporting on regression specifically in MUP patients reveal that approximately 12.4% of cases are associated with regression either before or after the diagnosis of MUP (6, 11–13).

The spontaneous regression of melanoma is likely immune-mediated, including both cell-mediated and humoral immune mechanisms (10). Regressing melanomas are characterized by increased numbers of tumor-infiltrating lymphocytes, which also confer a favorable prognosis (14, 15). Immune responses to melanoma-associated antigens are also mediated through cytotoxic T-lymphocytes (16). In addition, there is a high prevalence of melanoma-specific antibodies in the serum of MUP patients, and various humoral immune mechanisms, including antibody attachment to cell membranes, cytotoxicity, and tumor destruction, have all been described with cultured melanoma cells *in vitro* (12, 17–22).

Alternatively, MUP could also be explained by the presence of ectopic melanocytes or the differention of melanocytes from preexisting pluripotent stem cells within subcutaneous tissue, LNs, or visceral organs (4). Melanocytes are derived from the neural crest, and they migrate along dorsolateral pathways during embryogenesis to reach the skin and hair follicles (23). Melanocytes also migrate to the inner ear, the leptomeninges, and the uveal tract of the eye, which includes the choroid, ciliary body, and iris (23). Occasionally, melanocytes are also found

in other mucosal sites, including the conjuctivae, nasopharyngeal mucosa, esophagus, and anorectal mucosa (23). Regarding LNs, benign nevus cell aggregates and blue nevi have been reported in LNs and other tissues, and, interestingly, melanoma arising from ectopic melanocytes within a LN has been reported (24–27). Thus, melanoma discovered in LNs may originate from the malignant degeneration of neural crest–derived melanocytes that migrated and became arrested in LNs or, alternatively, from benign nevus cells that migrated from the skin to the draining LNs.

In addition, some investigators have questioned whether reports of MUP diagnosed in visceral organs may actually represent primary melanomas arising in unique anatomic locations. For example, the gastrointestinal tract is a common metastatic site for cutaneous melanoma and is also the most widely described visceral site for MUP (3, 28). It has been postulated that cases of gastrointestinal MUP may actually represent cases of primary melanoma derived from melanoblastic cells of the neural crest (28). Melanoblastic cells are known to migrate to the small intestine, predominately the ileum, through the omphalomesenteric canal (28). These melanoblastic cells differentiate into ectopic melanocytes of the gastrointestinal tract, which could theoretically under rare circumstances form primary gastrointestinal melanomas (28). Finally, there is confusion in the literature regarding MUP presenting within the adrenal gland. The adrenal medulla contains neuroendocrine cells derived from the neural crest, and it is thought by some that MUP diagnosed in the adrenal gland should instead be referred to as primary adrenal melanotic malignant pheochromocytoma (29).

GENETICS

The genetic profiles of cutaneous, acral, ocular, and mucosal melanomas differ significantly. Recent studies have examined the genetic profile of MUP (30). Specifically, MUP shares many of the genetic and molecular signatures of melanoma arising from intermittently sun-exposed sites on the skin, including the back and upper legs (Table 2) (31–33). An analysis of 102 MUP patients after therapeutic lymphadenectomy revealed that BRAF and NRAS mutations occurred in 53 and 14% of MUP specimens, respectively (31). Of note, BRAF V600E mutations compromised 93% of all BRAF mutations in this MUP cohort, and no c-KIT mutations were identified (31). Thus, the genotype of MUP most closely resembles that of cutaneous melanoma, specifically the superficial spreading and nodular histological subtypes arising from intermittently sun-damaged skin (33, 34). This genetic signature is distinct from cutaneous melanoma arising from chronically sun-damaged skin, acral skin, and mucosal sites, which are commonly enriched for c-KIT mutations (34). In a separate analysis of 39 MUP patients, mutations in the TERT-promoter were found more commonly in MUP than in mucosal melanoma (66.7% vs. 13.2%, respectively) (35). The presence of TERT-promoter mutations in MUP tumors correlated with a higher percentage of BRAF and NRAS mutations, leading to the hypothesis that TERT-promoter mutations may function as driver mutations in MUP (35).

INCIDENCE AND DEMOGRAPHICS

Likely related to the inherent difficulty in defining MUP, the incidence of MUP is widely reported, ranging from 1.2% to as high as 31% (36–38). Recently, a large systematic review clarified the true incidence of MUP and reported an overall incidence of 3.2%, which remained stable when children and adolescents were excluded from the analysis (3). The wide incidence range previously reported in the literature could also be partly explained by the improving technology of medical imaging, which can lead to enhanced identification of the primary tumor (3). In the above systematic review, the incidence of MUP before the modern computed tomography era (3) in 1980 was 5.1%, as compared to 2.7% after 1980 (3).

The peak incidence of MUP occurs in the fourth and fifth decades of life, comparable to cutaneous melanoma, but earlier than mucosal and ocular melanoma (1, 39). The younger age of MUP peak incidence may be attributed to the robust immune responses of younger patients, resulting in a higher rate of primary site regression (3). Moreover, MUP occurs twice as often in men as in women, and this has been attributed to epidemiologic factors related to an increased likelihood for primary site regression (3). For example, men may be more likely to ignore a primary cutaneous melanoma until after it completely regresses and later presents as metastatic disease, and men are also more prone to developing melanoma in anatomic sites where regression may be more likely to occur, including the back and scalp (3).

METASTATIC SITES

MUP is most commonly diagnosed in LNs (40–60% of all cases) and has been reported to involve the axillary, cervical, inguinal, and parotid LNs in 52.2, 32.7, 28.3, and 2.6% of cases, respectively (3, 13, 40). In men, MUP most commonly presents in axillary and cervical LNs, whereas in women it is most likely to present in inguinal LNs (3). The higher incidence of inguinal LN involvement in women compared to men has been attributed to the higher incidence of leg and anogenital melanoma in women (4).

After the LNs, MUP is diagnosed most commonly in subcutaneous sites (approximately 30% of cases) and is least commonly diagnosed in visceral organs (approximately 20% of cases) (3, 13). In the recent systematic review of MUP, 5.1% of patients presented with subcutaneous involvement, 4.9% with single or multiple visceral sites, and 0.7% with osseous deposits (3). A multitude of visceral sites are reported with MUP, including the brain, parotid gland, heart, mediastinum, lung, breast, liver, common bile duct, small and large intestine, kidney, adrenal gland, prostate, bone, bone marrow, and muscle (29, 41–65). As expected, varying clinical presentations of visceral disease are described in the literature depending on the involved organ (Table 3) (46, 49, 59, 66–72). MUP can also present as a paraneoplastic syndrome, reported as retinopathy, systemic vasculitis, inflammatory demyelinating polyneuropathy, diffuse vitiligo-like depigmentation, and Gorham-Stout syndrome, or vanishing bone disease (73–78). Vitiligo-like depigmentation appears to be a fairly common presentation of widespread metastatic disease and can precede the discovery of MUP by up to 18 months (76, 79, 80).

TABLE 3 Varied clinical presentations reported for melanoma of unknown primary (46, 49, 59, 66–72)

Involved visceral organ	Clinical presentation
Colon (47, 50, 53, 66, 67)	Intestinal obstruction Intussusception Gastrointestinal bleeding Bowel perforation
Kidney (54)	Hematuria
Heart (59, 69)	Pericardial effusion Heart failure
Liver (46, 68)	Hepatosplenomegaly Fulminant liver failure
Sacrum (70)	Radiculopathy
Brain (55, 72)	Acute meningitis Seizures
Bone marrow (49, 62)	Thrombocytopenia
Seminal vesicles (71)	Hematospermia

A few special considerations regarding visceral involvement should be emphasized. First, the original primary melanoma can become clinically evident after the diagnosis of MUP. For example, Kumar et al. reported the case of a 56-year-old woman with MUP diagnosed in a left axillary LN who presented with a primary cutaneous melanoma of the left finger 18 months after the original MUP diagnosis (81). Second, MUP can present with varied histological appearances, which can often complicate the pathologic diagnosis, and underscore the importance of immunohistochemistry in making a diagnosis of MUP. MUP has been described as a signet-ring cell neoplasm with abundant intermediate filaments that was only recognized as a melanocyte neoplasm when it stained positive for vimentin, S-100, and HMB-45 (82). Similarly, Adler et al. described the case of an angiomatoid melanoma mimicking a vascular malignancy, characterized histologically as a spindle cell tumor with numerous cavernous, erythrocyte-filled spaces, and only scant melanin pigmentation (83).

STAGING AND PROGNOSTIC FACTORS

The prognostic factors of patients with MUP are similar to those of MKP with the same clinical stage at presentation (84–86). However, until recently, no uniform staging guidelines existed for MUP (8, 87, 88). In 2009, the American Joint Committee on Cancer (AJCC) melanoma staging system classified MUP as stage III disease if there were LN or subcutaneous involvement at initial presentation, and as stage IV disease if there were visceral involvement (89). Serum S100 protein and positron emission tomography (PET) are recommended for baseline staging

of MUP patients (90). In one study, serum S100 protein was elevated in 35% of MUP patients, and PET scans detected occult distant metastases in 86% of MUP patients (90). In addition, distant metastases were associated with significantly higher serum S100 proteins levels, suggesting that serum S100 protein may be a sensitive and specific marker to detect occult distant metastatic disease in MUP patients (90).

Similar to MKP, the patient's age, AJCC stage, lactate dehydrogenase level, and number of metastases at diagnosis are all independent prognostic factors for MUP (91). Furthermore, in multivariate analyses stratified by AJCC stage, in-transit metastases and number of involved LNs are independent prognostic factors for stage III disease, and age and lactate dehydrogenase level at diagnosis are independent prognostic factors for stage IV disease (91). Additional positive prognostic factors for MUP include evidence of tumor regression, fewer numbers of involved LNs, and prompt surgical treatment within 3 months (3, 86, 91–93). Moreover, four studies reported a better prognosis for younger patients, but the effect of gender on prognosis is yet to be fully elucidated (3, 36, 91, 94, 95). Negative prognostic factors include the involvement of cervical LNs, extracapsular extension, and the presence of in-transit metastases (86, 88, 91, 96, 97). Ultimately, LN involvement was identified as the most important prognostic factor in MUP (97). Specifically considering only stage IV disease, an increased number of metastatic sites and lactate dehydrogenase at presentation were both associated with significantly worse outcomes (91).

Concerning mutational status, the presence of BRAS, NRAS, and TERT-promoter mutations do not appear to have a significant prognostic impact, as there is no correlation between mutational status and overall survival (OS) for MUP patients (31, 33). Interestingly, MUP patients with vitiligo may have improved survival (13, 98). For example, vitiligo was diagnosed in 5 of 88 MUP patients in one cohort, and the presence of vitiligo was associated with a favorable prognosis (13). Another study described prolonged survival associated with the development of vitiligo 6 years after the diagnosis of MUP in axillary LNs (99). In this case report, there was no recurrence of melanoma 10 years after surgical resection of the involved LNs (99).

SURVIVAL

Median OS ranges from 24 months to 127 months for MUP patients presenting with LN disease (AJCC stage III), with 5- and 10-year OS ranging from 28.6 to 75.6%, and 18.8 to 62.9%, respectively (3, 39). The OS of stage III MUP is significantly better than MUP patients with visceral stage (AJCC stage IV), with median OS ranging from 3 to 13 months, 5-year OS ranging from 5.9 to 18%, and no 10-year survivors (3, 39). In a systematic review of MUP, seven studies demonstrated a significantly better prognosis for nodal MUP, compared to subcutaneous or visceral MUP (1, 8, 11, 91, 95, 100, 101). Regarding the effect of surgical management on survival, prompt radical neck LN dissection led to improved survival in three studies, while modified radical neck LN dissection led to improved survival in just one study (1, 8, 102, 103). However, the prognostic advantage of modified versus radical neck LN dissection could not be

conclusively determined in the systematic review (3). Similar to stage III MKP, non-surgical management of stage III MUP is associated with worse survival compared to surgical management (3). Some investigators suggest that surgery not only decreases the overall tumor burden but also decreases the degree of immunosuppression, allowing anti-tumor immunity to develop (3).

Survival of MUP compared to MKP patients

Several studies attempting to compare survival differences between MUP and MKP patients utilizing matched patients and historical controls have revealed mixed results. As early as 1998, Vijuk and Coates reported a median survival of 233 days for MUP patients, compared to 176 days for MKP patients (104). Similarly, Prens et al. examined outcomes of MUP patients after therapeutic neck LN dissections and found a trend for improved survival in MUP compared to MKP patients with 5-year OS of 40 and 27%, respectively (105). More recently, Weide et al. also reported improved OS for MUP patients compared to MKP patients with LN involvement (median OS 65 months vs. 24 months, respectively) (96, 97). Regarding stage IV disease, a retrospective analysis of 534 patients with stage IV MUP and a median follow-up of 10.4 months revealed that MUP patients had a similar survival as cutaneous melanoma and uveal melanoma from the time of first distant metastasis but significantly better survival than mucosal melanoma (106).

A statistically significant survival difference between MUP and MKP patients has been demonstrated in only a handful of published studies (3). Lee et al. reported a significantly higher 5-year OS for MUP patients compared to MKP patients when matched for nodal metastases, site of metastatic disease, and number of metastatic sites (36, 39). Matching stage III patients based on four additional covariates, including age, sex, nodal tumor burden, and decade of diagnosis, also revealed a significantly higher median OS for MUP compared to MKP patients (164 months vs. 34 months, respectively) (39).

In an attempt to clarify the prognosis of MUP compared to MKP patients, Bae et al. recently conducted a meta-analysis of all studies reporting on survival to date, and reported better OS for stage III MUP patients compared to MKP patients (hazard ratio 0.83, 95% confidence interval 0.73–0.96, P = 0.01) and stage IV MUP patients compared to MKP patients (hazard ratio 0.85, 95% confidence interval 0.75–0.96, P = 0.08) (107). Subgroup analyses also showed that MUP patients with nodal disease only had improved OS (hazard ratio 0.82, 95% CI 0.71–0.95) and disease-free survival compared to MKP patients (hazard ratio 0.84, 95% CI 0.70–1.00) (107). The improved survival of stage III and stage IV patients MUP compared to MKP patients is particularly striking given that lead-time bias should inherently favor a survival benefit for MKP patients because the presence of a known primary would likely lead to an earlier diagnosis of each disease stage.

DIAGNOSIS

A thorough evaluation, including ophthalmologic and anogenital exams, is required when melanoma is diagnosed within the subcutaneous fat, LNs, or visceral organs

without an obvious primary source. However, the exact type of work-up that is recommended for MUP patients after a complete physical examination is controversial (Figure 1). In one study of 103 MUP patients, Tos et al. found that 84% of patients were examined by an ophthalmologist, 82% by an otorhinolaryngologist, and 89% by a gynecologist (108). Moreover, 92% of MUP patients had additional gastrointestinal imaging performed, including sigmoidoscopy and proctoscopy (108). Of the additional referrals and evaluations performed in this particular study, the only primary site discovered was that of an undiagnosed choroidal melanoma (108). Based on these findings, this group recommended a detailed history, physical examination, histopathologic review, and CT and/or PET for accurate staging for all new MUP patients but suggested that additional subspecialty referrals and specialized screenings may be redundant (108).

Similarly, a worldwide survey of 119 providers in 47 countries analyzed the clinical and laboratory work-up required for MUP patients after a thorough history and physical examination (109). Half of all responders specifically assessed for the presence of vitiligo that may help explain regression of the primary site (109). Three-quarters of all responders applied the same protocols for MUP patients as AJCC stage-matched MKP patients (109). In addition, all responders asked about the history of previous skin excisions, and 81% reviewed histopathologic slides from prior biopsies (109). Specifically, histopathologic review by an experienced pathologist is essential, as MUP can mimic other spindle cell neoplasms. For example, MUP of the parotid gland mimicked an interdigitating dendritic cell sarcoma, and ultimately required immunohistochemical staining to accurately

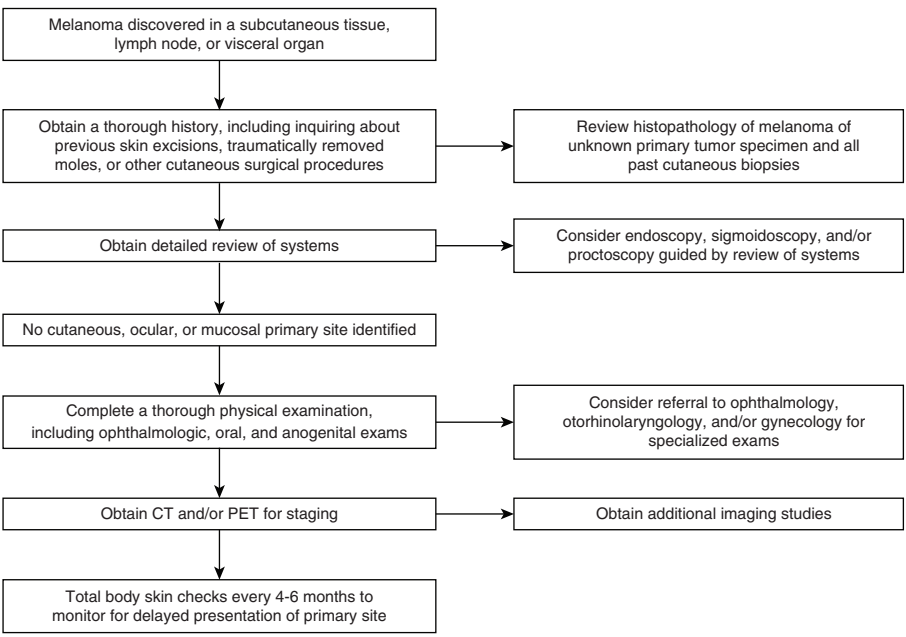

Figure 1 Work-up for newly diagnosed melanoma of unknown primary.

identify the melanocytic origin of the tumor (110). In another case, hilar and mediastinal masses were initially highly suggestive of a primary lung cancer radiographically but were ultimately discovered to be S100-negative MUP after histological analysis (111).

In addition, long-term follow-up is essential, as the occult primary can become clinically apparent over 5 years after the original diagnosis of MUP. In one case report of MUP diagnosed in the liver and treated with chemotherapy and radiation, the most likely primary, a nasopharyngeal mucosal melanoma, only became clinically apparent 6 years after the original MUP diagnosis because of new onset epistaxis (112). In another case report of MUP diagnosed in the small intestine, the most likely primary became clinically apparent on the scalp 15 years after the original MUP diagnosis (113). These delayed primary site presentations may have resulted from incomplete physical examinations at the time of initial MUP diagnosis, or they could relate to alterations in the patients' immune responses, resulting in growth of the primary tumor to the point of becoming clinically apparent.

Molecular profiling, imaging, autoantibodies, and dermoscopy can be used for the accurate diagnosis of MUP (114, 115). In the above survey study, 32% of respondents also screened MUP tumor specimens for BRAF, c-KIT, and GNAQ mutations, and the most common imaging modalities utilized were CT and/or PET (109). Furthermore, transient receptor potential melastatin 1 (TRPM1) autoantibodies may be useful in the work-up of MUP (116). Dalal et al. described a patient with bilateral intraocular inflammation and retinal hemorrhage concerning for melanoma-associated retinopathy whose initial work-up for melanoma was unrevealing (116). Subsequently, the patient was found to have positive TRPM1 autoantibodies, which then prompted additional imaging that revealed an occult MUP involving an axillary LN (116). Finally, various groups have suggested that dermoscopy should be used to systematically narrow the field of potential candidate pigmented lesions for biopsy, and to identify subtly atypical pigmented lesions in order to diagnose an occult primary melanoma (115, 117).

MANAGEMENT

Numerous case series have supported the consensus that MUP patients should be treated with early aggressive surgical management in a similar fashion as MKP patients (6, 8, 100, 102, 118, 119). Most recently, a cohort of 78 MUP patients with LN or subcutaneous disease treated with regional lymphadenectomy or wide local excision further supports these early treatment recommendations (120). Although the local recurrence rate of subcutaneous disease after wide local excision with one to two centimeter margins was relatively high at 65%, the authors concluded that wide local excision still remains the best treatment option for subcutaneous disease (120). In contrast, the significantly lower local recurrence rate of 11% for LN disease after regional LN dissection substantiates its use as the standard of care for MUP with LN involvement (120).

Moreover, regional lymphadenectomy for palpable LN metastases was associated with significantly improved 5-year OS for stage III MUP patients compared to MKP patients (39). When patients were matched based on age, sex, nodal

tumor burden, and decade of diagnosis, the median OS was 164 months for MUP patients compared to 34 months for MKP patients (39). Similar findings were confirmed in a separate cohort of MUP patients, which also demonstrated improved disease-free, distant metastases-free survival, and melanoma-specific survival for MUP patients compared to MKP patients after therapeutic LN dissection (121). Extranodal extension, greater than three positive LNs, and adjuvant radiotherapy were all independent predictors of reduced disease-free and melanoma-specific survival in MUP patients (121). Thus, the absence of a primary site should not preclude aggressive surgical management with regional lymphadenectomy in stage III MUP patients, and these patients should also be considered for adjuvant therapies traditionally aimed at stage III MKP patients (105, 122, 123).

These findings were confirmed in the systematic review of MUP performed by Kamposioras et al. (3). Wide local excision or LN dissection, either radical or modified, combined with parotidectomy, if necessary, is the current standard of care for surgical management of stage III MUP (3). Stage IV MUP also warrants aggressive therapy, and it should be treated similarly to stage IV MKP with a combination of surgery, chemotherapy, immunotherapy, and radiotherapy, as the median OS and 5-year OS for stage IV MUP is significantly higher than stage IV MKP when matched for the site of metastatic involvement (36).

CONCLUSION

MUP, defined by the presence of melanoma in distant subcutaneous sites, LNs, or visceral organs without an obvious cutaneous, ocular, or mucosal primary site, is a well-characterized entity in the literature. It comprises 3.2% of all new melanoma diagnoses and occurs more commonly in men with a peak incidence in the fourth and fifth decades of life. LN involvement occurs more often than subcutaneous or visceral disease and most commonly affects the axillary LNs. Furthermore, involvement of a wide variety of visceral organs has been reported with MUP, and the possibility of primary noncutaneous melanomas occurring as a result of the malignant degeneration of ectopic melanocytes present in visceral organs, including the gastrointestinal tract, should be considered.

MUP should be classified as AJCC stage III disease if it is diagnosed in LNs, or as subcutaneous tissue at initial presentation, or as AJCC stage IV disease if it is diagnosed in visceral organs. MUP patients have better prognoses and improved OS compared to stage-matched MKP patients, suggesting that immunologically mediated primary site regression may be the common underlying mechanism explaining the biological phenomenon of MUP. Given their improved survival, patients with stage III MUP should be treated with wide local excision for subcutaneous disease, and modified or radical LN resection for LN disease, and these patients should be offered enrollment in clinical trials as well as similar adjuvant therapy as stage III MKP patients. Finally, patients with stage IV MUP should be treated aggressively and similarly to patients with stage IV MKP, with combination of surgery, chemotherapy, immunotherapy, and radiotherapy.

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