Although, malignant melanoma accounts for 3% of skin cancers, it is responsible for 75% of deaths associated with skin cancer. In our study, all melanoma cases diagnosed and treated at our clinic were reviewed retrospectively, and the cases of unknown primary origin among them were examined in detail in terms of diagnosis and treatment. The malignant melanoma patients treated at the inpatient services of our clinic in the period between January 1991 and April 2017 were screened in the records retrospectively. These patients were evaluated for age, sex, tumor type, Breslow, metastasis, and treatment. Among these patients, 4 cases of unknown primary origin were examined in detail. During the period between January 1991 and April 2017, 173 patients received inpatient care at our clinic due to malignant melanoma. As regards to the melanoma subtypes, nodular type in 45 patients, acral lentiginous type in 43 patients, superficial spreading type in 63 patients, lentigo maligna melanoma in 15 patients, subungual type in 7 patients, and either unidentified melanoma or other subtypes in 10 patients were identified. The ideal treatment of a melanoma patient is multidisciplinary, with plastic surgery having a central role. The objective of the study was to demonstrate variabilities, rendering the condition complicated. Although more than 95% of cases of melanoma originate from skin; some melanoma cases of unknown primary origin may be observed involving lymph nodes or visceral organs without any foci on the skin. In our study, all melanoma cases diagnosed and treated at our clinic were reviewed retrospectively, and the cases of unknown prima-
ry origin among them were examined in detail in terms of diagnosis and treatment.

**Methods**

The malignant melanoma patients treated at the inpatient services of our clinic in the period between January 1991 and April 2017 were screened in the records retrospectively. These patients were evaluated for age, sex, tumor type, Breslow depth, metastasis, and treatment. Among these patients, 4 cases of unknown primary origin were examined in detail.

**Results**

During the period between January 1991 and April 2017, 92 males and 81 females comprising a total of 173 patients, received inpatient care at our clinic due to malignant melanoma. The age of the patients ranged between 2-82, and the mean age was calculated as 52.56. A mass was detected in the head and neck region of 48 patients, on lower extremities of 69 patients, on the trunk of 29 patients, on upper extremities of 18 patients, and in the genital area of 7 patients (Fig. 1). As regards to the melanoma subtypes, nodular type in 45 patients, acral lentiginous type in 43 patients, superficial spreading type in 63 patients, lentigo maligna melanoma in 15 patients, subungual type in 7 patients, and either unidentified melanoma or other subtypes in 10 patients were identified. Breslow value was measured 0-1 mm in 19 patients, 1-2 mm in 35 patients, 2-4 mm in 68 patients, and deeper than 4 mm in 39 patients, while in 12 patients, breslow could not be evaluated. Sentinel lymph node sampling in 51 patients, axillary lymph node sampling in 26 patients, inguinal lymph node sampling in 57 patients and lymph node sampling at neck area in 25 patients were performed, comprising a total of 108 regional lymph node dissection cases. With regard to the defects developed after tumor resection, primary suturing in 11 patients, partial or complete digital amputation in 12 patients, local or distant flaps in 41 patients, and partial or full thickness grafts in 119 patients were performed for reconstruction. Contacting patients or their relatives revealed that of 124 patients; 47 died, 75 lived uneventfully, and 2 were in the terminal period.

**Case 1**

A fifty-two-year-old male patient presenting with the complaints of vomiting, weight loss, and abdominal pain received treatment at a health center but as the complaints continue he underwent abdominal ultrasonography revealing intestinal thickening. Then, a contrasted intestinal scopy was performed demonstrating a mass of 7.5x2.5 centimeter in size. Following this finding, the patient underwent a segmental resection of the small bowel. As the pathological examination determined metastasis of melanoma, the patient was referred to the oncology department at our hospital. To screen for the primary focus postoperatively; gastroenterology, ophthalmology, dermatology, and ENT (Ear, nose, throat) consultations were received together with endoscopy and colonoscopy examinations of the gastrointestinal system. However, a primary focus was not identified. During the postoperative follow-up period, an intramuscular metastatic lesion of 12x6x6 mm in size adjacent to biceps femoris muscle in the posterior part of the left lower extremity was detected in the whole body PET CT. Due to this finding, primarily an excisional biopsy of the mass was performed. As the pathological examination result was metastasis of melanoma, the patient had received a temodal treatment for 9 months. During the follow-up period, a mass was identified on the medial side of the right knee joint. Following an incisional biopsy revealing melanoma metastasis, left inguinal sentinel sampling and left popliteal dissection were performed (Fig. 2). As metastasis in the inguinal and popliteal regions was reported as the result of the pathological examination, the patient underwent additional inguinal dissection. Limb perfusion treatment was given to the patients by the oncology team. The patient was monitored at the follow-up visits, however, he died in the 5th year following the diagnosis.

**Case 2**

A twenty-nine-year-old male patient presenting with a groin mass in the inguinal region for one year, started an-
tibiotic therapy at a health care center. As there was no regression in the mass, an excisional biopsy was performed. The patient presented to our outpatient clinics with the biopsy result reporting metastasis of malignant melanoma. A PET CT was performed and the pathology specimens were re-evaluated at our hospital. In addition, the patient was consulted by the dermatology clinic preoperatively for his additional skin lesions. No additional focus was identified and the patient underwent inguinal curettage. To screen for the primary focus postoperatively; gastroenterology, ophthalmology, dermatology, and ENT consultations were received together with endoscopy and colonoscopy examinations of the gastrointestinal system. However, the primary focus was not detected. The patient has been given interleukin treatment by the oncology team and he has continued his follow-up visits at our clinic.

**Case 3**
A forty-nine-year-old female patient presenting with a mass in the left inguinal region for two years, was followed up on medical treatment at a health care center for 6 months. As there was no relief in her complaints, she was referred to another facility. Following an excisional biopsy, the patient was referred to our clinics with the biopsy result reporting melanoma infiltration. A PET CT was performed and the patient was consulted by the dermatology clinic preoperatively for his additional skin lesions. Both examinations resulted in no evidence of any other foci. Then, an inguinal lymph node dissection was performed. To screen for the primary focus postoperatively; gastroenterology, ophthalmology, dermatology, and ENT consultations were received together with endoscopy and colonoscopy examinations of the gastrointestinal system. However, a primary focus was not detected. Because a BRAF mutation was detected, the patient was given vemurafenib treatment by the oncology team. She has been followed up at the oncology clinic and at our facilities.

**Case 4**
A 46-year-old male patient presenting with a hypertrophic lesion in the heel was administered cryotherapy at a dermatology clinic. As there was no relief in his complaints, a
punch biopsy was performed reporting a melanoma infiltration. Then, the patient was referred to our clinics. A PET CT was performed and the patient was consulted by the dermatology clinic preoperatively for his additional skin lesions. The lesion in the heel was excised within adequate surgical margins, and then was repaired by a vastus lateralis free flap. (Although ALT was planned initially, the vastus lateralis muscular flap was performed as the patient’s skin perforators were not sufficient) (Fig. 3). The pathological examination reported an infiltration of malignant melanoma (Fig. 4a-d). To screen for the primary focus postoperatively; gastroenterology, ophthalmology, dermatology, and ENT consultations were received together with endoscopy and colonoscopy examinations of the gastrointestinal system. But, a primary focus was not evident.

Four patients with melanoma metastasis as a result of pathology were investigated in terms of finding the primary lesion (Flowchart); however, the primary focus could not be determined. These patients were examined in detail in terms of diagnosis and treatment (Fig. 5).

Discussion

Malignant Melanoma (MM) originates from melanocytes, a subtype of the dendritic cells or from nevus cells in the basal layer of the skin. Melanocyte cells are not only limited to the skin, but may be present in the eyes, upper respiratory tract, gastrointestinal tract, normal lymph node capsules, and central nervous system. Therefore, a primary melanoma can originate from those sites. More than 95% of ma-

Figure 4. (a) Melanocytes with prominent nucleus and nucleoli and condensed chromatin arranged in nests and individually in the sclerotic dermis with no continuity with the overlying epidermis. H&E, x200. (b) Melanocytes with prominent nucleus and nucleoli and condensed chromatin arranged in nests and individually in the sclerotic dermis, H&E, x400. (c) Melanocytes strongly stained with HMB45 within the sclerotic dermis. Note that the stratified squamous epithelium is unremarkable. HMB-45 stain, x100. (d) Weakly positive stained melanocytes with Melan A within the sclerotic dermis. Melan A, x200.
Ligant melanoma cases are observed in the skin covering the body. Cutaneous melanoma is the type of cancer with a rising incidence in the Caucasian population in the world, and is responsible for 75% of deaths from skin cancer. Melanoma metastases are observed in local lymph nodes; or develop as satellite or in transit lesions, or become evident as distant organ metastasis. A study conducted at the University of Tuebien reviewed melanoma cases in a 20-year period retrospectively, and reported metastases in 466 of 3001 patients. 50% of the metastases were detected in the lymph nodes, 22% of them were satellite or in transit metastases, and 28% of them were distant organ metastases including distant metastases in skin. In our clinic, in a total of 173 patients, regional lymph node, satellite, and in transit metastases were evident in 34, 3, and 2 patients respectively. When distant metastases of primary melanomas were evaluated, cutaneous melamnomas were identified to develop distant metastases to lung most commonly. The influencing factors in melanoma metastasis are the region of the primary tumor most commonly, followed by the gender and age of the patient, histology findings, tumor depth, and the extent of invasion. Satellite or in transit metastasis rates are higher in lesions of the extremities and trunk. However, all three ways of metastasis are observed with the melanomas in head and neck. In regards to tumor thickness, values lower than 0.76 mm and over 1.5 mm are associated with higher rates of satellite and in transit metastases, and thickness values between 0.75-1.5 mm are related with higher rates of distant metastases. When the timing of metastasis is evaluated, it requires a mean of 25 months for distant metastases, a mean of 17 months for satellite or in transit metastases, and a mean of 16 months for lymph node metastases.

Malignant melanoma of unknown primary origin or otherwise called occult melanoma was identified by Pack in 1952 as a patient with a diagnosis of subcutaneous, nodal, or visceral metastatic melanoma without an identified cutaneous, ocular, or mucosal primary origin, and who had no history of histological examinations or excisions. Melanoma of an unknown primary origin is usually diagnosed when clinical symptoms due to metastasis become evident. In 1963, Das Gupta defined the exclusion criteria in the differential diagnosis of malignant melanoma. According to these criteria, the patients should be excluded from the differential diagnosis if they have a history of previous orbital exenteration or enucleation, if there is a history of excision, electrodesiccation or cautery rendering a retrospective pathological examination inadequate, and if patients with lymph node metastases have scars in the region where drainage occurred and if they are evaluated neither by a detailed physical examination including anus and genital area nor by ophthalmoscopy.

Several theories have been proposed for the development of melanoma of an unknown origin. These theories pro-
vided the following explanations including the regression associated with immune response following metastasis of the primary tumor, melanoma developing in nevus cells of lymph nodes, metastasis of an undetected tumor in the body, misdiagnosis of the previous excision material, and presence of a primary tumor in an unusual or shrouded region. The most commonly recognized theory is the regression of the primary lesion due to stimulation of immune system.

The study by Kamposiras et al. reviewed all melanoma cases published in literature till 2010, and reported melanoma of unknown primary origin in 4348 of 136,991 melanoma patients. According to this study the incidence of melanoma of unknown primary origin was determined as 3.2%. In this study, the period before 1980, which is the year when CT was implemented into practice and the period after CT implementation were compared demonstrating incidences of 5.05% and 2.7% for the pre-CT and post-CT periods respectively. The same study reported the ratio of male patients to female patients 2/1 (2948/1454). Savoia et al. reported 88 patients with melanoma of unknown origin in their 33-year study with a series of 4481 melanoma patients. Of these 88 patients, metastases were detected in skin and subcutaneous tissue in 31 patients, in the lymph nodes in 48 patients, and in visceral organs in 15 patients. The rate of melanoma of unknown origin of our clinic is 0.02% with 1 patient having a visceral metastasis, 2 patients with lymph node metastases, and 1 patient with a metastasis in lower extremity.

For patients with melanoma of unknown origin, in order to identify the primary lesion, it is recommended that all previous excision materials should be examined in detail for melanoma in first place, gastrointestinal endoscopy, endoscopic examination of nose and larynx, otoscopy, ophthalmoscopy, and a detailed physical examination including anus and genital area should be performed, female patients should be examined gynecologically, and CT scans of brain, neck, thorax, and abdomen must be obtained. A Wood lamp examination by UV light is warranted in cases with depigmented halo nevi and scars or in cases when a regressed melanoma is suspected. To screen for the primary lesion, all patients in our study were consulted with gastroenterology, ophthalmology, dermatology, and ENT postoperatively, and endoscopic and colonoscopic examination of GIS were provided, however no primary foci were evident. The female patient was consulted with the gynecology department additionally.

Initial treatment of patients with melanoma of unknown origin is surgery. Palliative or adjuvant treatment is administered in alignment with the planning made according to patients’ condition postoperatively. The medicine used for this treatment include interferon alpha 2b, IL-2, dacarbazine, temozolomide, BOLD regime (bleomycin, vincristine, lomustine, and dacarbazine).

The survival is more favorable in patients with melanoma of unknown origin. These cases are considered to be associated with an increased immune response to the metastatic lesion in return for the immune response so strong to regress the primary tumor. The literature review by Kamposiras et al. recognizes that for nodal metastasis of unknown primary origin the mean survival is between 24-165 months, whereas in visceral metastasis it is between 3-13.2 months. In addition, it is reported that in nodal metastasis 10 year survival rate is between 18.8%–62.9%, however in visceral metastasis no patients with a 10 year survival are evident.

**Conclusion**

Unknown primary melanoma are challenging for both surgeons and oncologist. Standard guidelines are not available because of its rarity. Case series are important in terms of guiding the physicians in the absence of these guidelines. Cooperative studies involving several treatment center are critical in these kind of rare tumors. Combination of these information can provide larger number of cases for better decision making.

**Disclosures**

**Ethics Committee Approval:** The study was approved by the Local Ethics Committee.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**References**


