Melanoma of Unknown Primary Origin: A Case Report and Literature Review

Ann. Ital. Chir., 2026: 1–17
https://doi.org/10.62713/aic.4214

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AIM: Melanoma of unknown primary origin (MUP) is a rare clinical entity, accounting for approximately 3–4% of all cases of melanoma. It is defined as histologically confirmed metastases of melanoma occurring in the absence of any identifiable primary lesion. Due to its rarity, diagnostic and therapeutic guidelines remain poorly defined. The aim of this literature review of published case reports is to investigate the most commonly affected anatomical sites, the most frequent presenting symptoms, the diagnostic approaches, and the available therapeutic strategies.

CASE PRESENTATION: 81-year-old woman was admitted with a right inguinal mass of unknown origin. Biopsy revealed metastatic melanoma involving the inguinal lymph nodes, with no clinically or radiologically detectable primary lesion. The patient underwent right inguinal–iliac–obturator lymphadenectomy. The postoperative course was uneventful, with no significant medical or surgical complications. Considering the patient's advanced age and overall condition, no adjuvant therapy was administered, and a strategy of active surveillance was adopted. At present, no evidence of disease recurrence has been observed.

RESULTS: A total of 94 case reports were included in our review. MUP appears to be more frequent in males than in females. The axillary lymph nodes were the most commonly involved site, followed by the cervical and inguinal lymph nodes. Among extranodal sites, the gastrointestinal tract, particularly the stomach and small bowel, was most frequently affected. Patients with MUP should be managed similarly to those with melanoma of known primary origin (MKP), based on corresponding stage and anatomical involvement.

CONCLUSIONS: MUP is an uncommon and challenging presentation of metastatic melanoma. Its pathogenesis remains unclear, although several theories, including immune-mediated regression of the primary lesion, have been proposed. MUP should be staged as stage IV disease and treated with the same systemic therapies used for stage IV MKP, including immune checkpoint inhibitors and targeted agents. Prompt recognition and standardized management are crucial to optimizing outcomes in this subset of patients.

Keywords: lymph node metastases; metastatic melanoma; melanoma of unknown primary origin; case reports

Introduction

Cutaneous melanoma represents an aggressive skin tumor derived from melanocytes. In Italy, it is the second most frequent cancer in males and the third in females [1,2]. In 1963, DASGUPTA *et al*. [3] first proposed a definition of melanoma of unknown primary origin (MUP). MUP is a rare clinical entity, accounting for only 3–4% of all metastatic melanoma cases, and is defined by the presence of melanoma metastases in lymph nodes, subcutaneous tissue or visceral organs without identification of a primary cutaneous, mucosal or ocular lesion. Despite its low incidence, MUP poses a significant diagnostic and therapeutic challenge due to the absence of a recognizable primary tumor and the lack of standardized treatment protocols [3–5]. The etiology of MUP is still unknown, although several theories have been proposed. The spontaneous regression of a primary cutaneous melanoma, likely mediated by the immune system, is the most widely accepted theory [6,7]. Understanding the origin of MUP is crucial for developing targeted treatment strategies and improving patient outcomes.

Submitted: 15 June 2025 Revised: 2 August 2025 Accepted: 19 August 2025 Published: 27 January 2026
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Editor: Sheng Dai

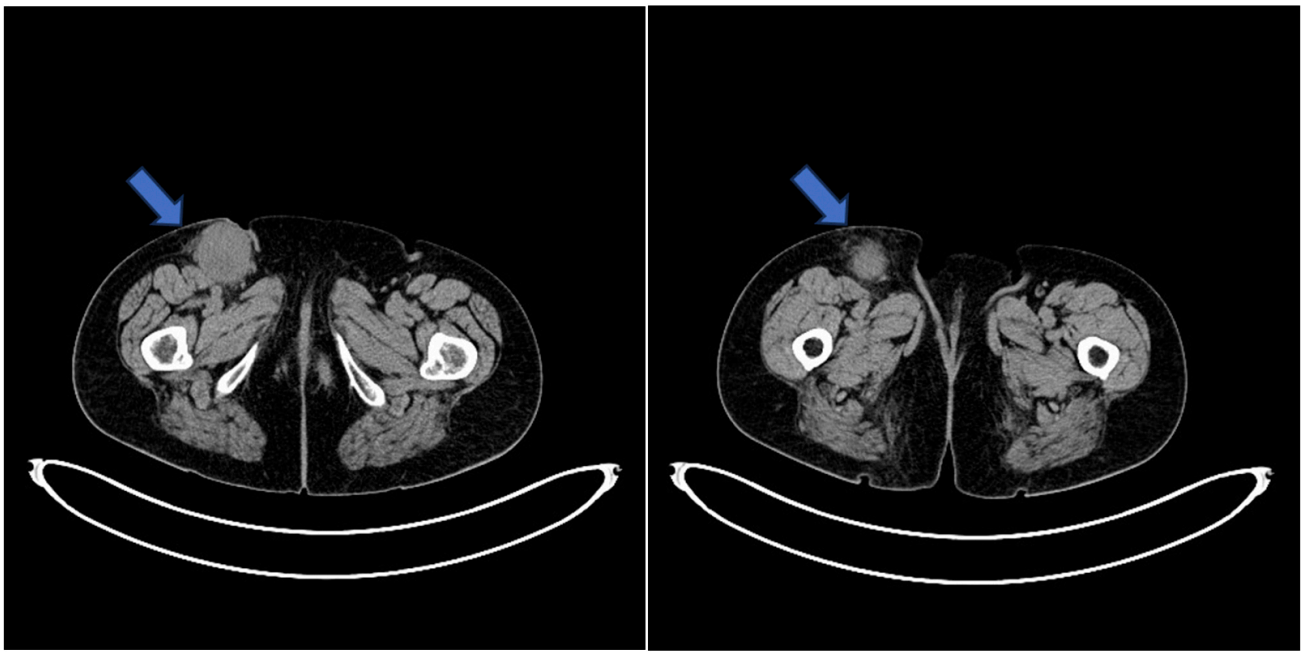

Fig. 1. The large right inguinal lymph node shown on the CT scan. The blue arrows highlight the presence of inguinal lymphadenopathy. CT, computed tomography.

In this paper, we present the case of 81-year-old woman with metastatic melanoma involving inguinal lymph nodes in the absence of an identifiable primary tumor. We also conducted a literature review with the aim of better defining the current clinical management of MUP, by evaluating the most commonly affected anatomical sites, typical presenting symptoms and the currently available therapeutic options.

Case Presentation

81-year-old woman was admitted to our emergency department for a right inguinal lesion of unknown origin. Her past medical history was unremarkable. The patient underwent an ultrasound scan followed by an incisional biopsy; the specimen was sent to pathology. Histology revealed the presence of a metastatic lymph-node from melanoma. The patient was referred to the Oncology Unit, and subsequently underwent a full medical work-up to determine the site of origin of the melanoma. A thorough dermatological examination did not reveal any suspicious primary lesions. The patient had no history of previous surgeries or excisions of skin lesions. Both genital and digital rectal examinations were negative. The patient also underwent ophthalmologic and ear, nose, and throat (ENT) evaluation, but no suspicious lesions were detected.

A full-body computed tomography (CT) scan was performed, showing negative oncological findings except for an isolated inguinal lymphadenopathy (Fig. 1).

During these investigations, the primary site of the melanoma was not identified, widespread metastases were detected at the level of the lymph nodes within the right Scarpa's triangle. Therefore, it was decided to proceed to surgery and the patient underwent an open right inguinal-iliac-obturator lymphadenectomy. A drain was placed and subsequently removed on postoperative day two, at the time of discharge. The following postoperative course was uneventful, with no significant medical or surgical complications.

Histological examination showed a single lymph node with "lymph node metastases (diameter 55 mm) of extensively necrotic neoplasm, consisting of epithelioid elements with prominent nucleoli, immunolabelled positive for sex determining region Y-box 10 (SOX-10), consistent with melanoma".

Due to the age of the patient, no adjuvant therapy was administered, and it was decided to continue only with active surveillance. The patient is currently 84 years old and has not experienced any lymph node or systemic recurrence. Written informed consent was obtained from the patient for the publication of this case report and accompanying images. The investigations were conducted in accordance with the principles outlined in the Declaration of Helsinki. The case report was conducted in accordance with the CARE (CAse REport) guidelines (**Supplementary Material**) [8].

Methods

We performed a case report review of MUP on the PubMed database with a return of 400 articles. Keywords used for identifying the case reports included: melanoma or cutaneous melanoma and melanoma of unknown origin or melanoma of unknown primary origin. We excluded those

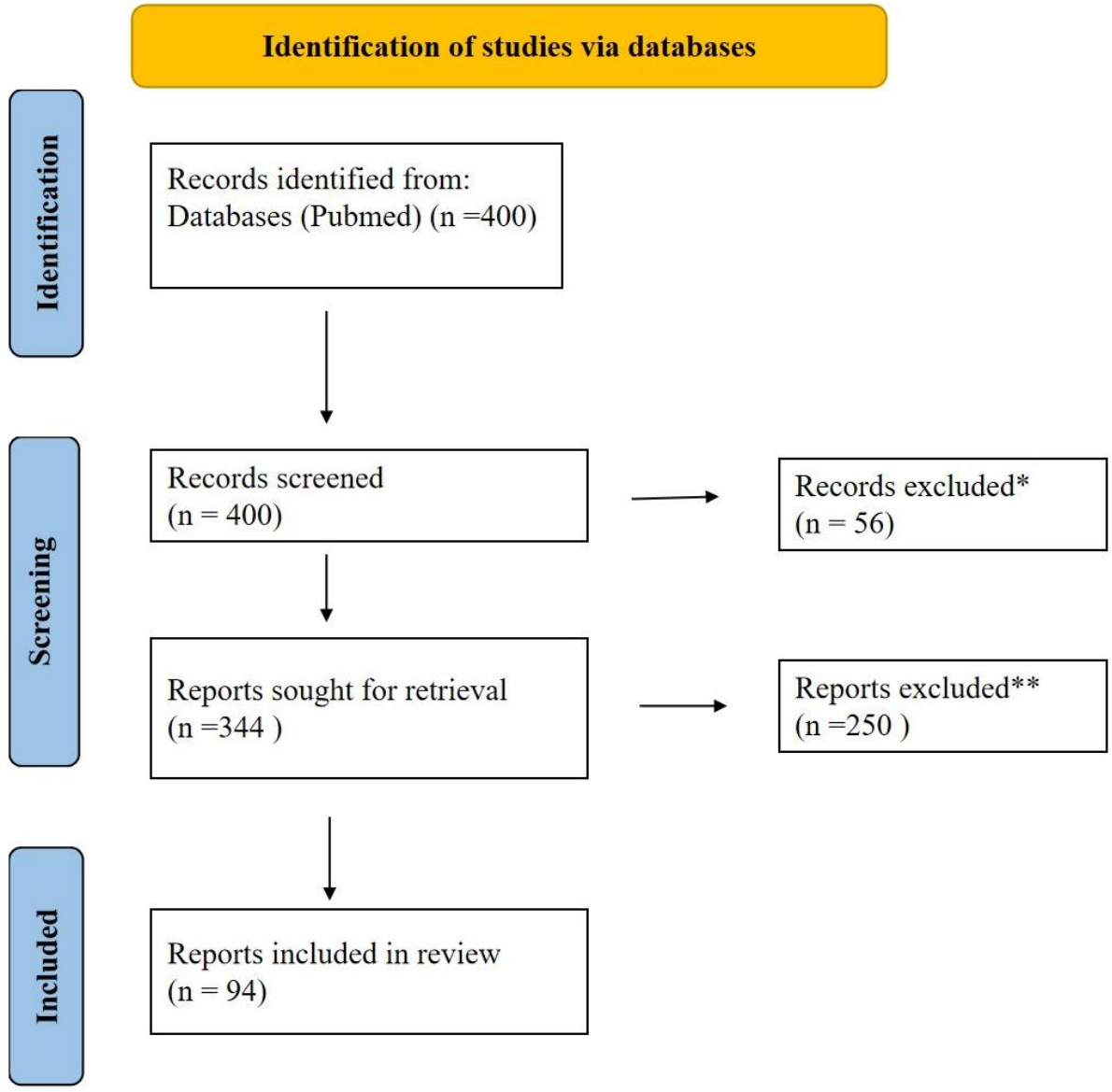

Fig. 2. The PRISMA flowchart of included studies. Records excluded*: exclusion of no-English written case reports; records excluded **: exclusion of no full text availability article, duplicate and no full text available. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

that were written in languages other than English, with 344 articles remaining. After a screening of the titles and abstracts by two term authors (MM and RC), and the exclusion of those without full-text availability, a total of 94 articles were included in our review (Fig. 2).

Results

A total of 94 [9–102] articles were included in our literature review. The exclusion criteria were language other than English, missing full-text publication, reviews, abstract from scientific meetings, letters and animal studies. The final search was completed in April 2025. The characteristics of patients and studies included are reported in Table 1 (Ref. [9–102]) and Table 2.

The analysis of case reports available in the literature shows that MUP, according to previous studies, is more frequent in males than in females. The axillary lymph nodes are the most commonly affected sites affected by MUP, followed by cervical and inguinal lymph nodes. Regarding extra-nodal involvement, gastrointestinal tract (particularly the stomach and small bowel) is the most common site of MUP, followed by the nervous system, subcutaneous tissue and bones and muscles. Some localizations, such as the breast, adrenal and salivary glands, pancreas and gallbladder involvement, are extremely rare: only sporadic reports have been documented in the literature. More information, especially about symptoms, is provided in the discussion section.

Table 1. Characteristics of studies included, and symptoms associated with MUP.

Authors	Age of patients	Sex	Symptoms	MUP site
Cortellini *et al*., 2021 [9]	81	M	Anemia, Anorexia Fatigue	Stomach
Jin *et al*., 2020 [67]	43	M	Upper abdominal pain	Pancreas
Andrianandrasana *et al*., 2023 [55]	43	M	Dyspnea Asthenia Weight loss Superior vena cava syndrome	Gluteus maximus Lateral, cervical lymph nodes
Takagi *et al*., 2020 [14]	77	M	Paresthesia Paraplegia	Spinal extradural, T6–T7
Kim *et al*., 2023 [47]	62	M	Cough Hemoptysis	Endobronchial
Phan *et al*., 2021 [19]	61	M	Palpable and painless lump	Lymph nodes, axilla
Yuan *et al*., 2023 [30]	61	M	Abdominal distension Nausea Weight loss	Liver
Grech *et al*., 2020 [56]	75	F	Excision of lump, suspected of a lipoma	Temporalis muscle
Rieth *et al*., 2021 [62]	69	F	Progressive loss of vision	Choroid
Bankar *et al*., 2015 [20]	41	F	Palpable and painless lump	Axillary lymph node Stomach
Rice-Canetto *et al*., 2024 [68]	72	M	Fatigue Left-sided weakness	Lung Brain metastasis
Proboka *et al*., 2018 [69]	58	F	Fatigue Dizziness	Craniospinal junction
Shan *et al*., 2009 [70]	62	F	Anorexia Abdominal distension	Liver
Bordeanu-Diaconescu *et al*., 2024 [87]	51	F	Infected hematoma	Left thigh
Nguyen *et al*., 2022 [36]	47	F	Status epilepticus	Brain
Dalle Carbonare *et al*., 2017 [57]	85	F	Trismus	Temporalis muscle
Suzuki *et al*., 2014 [54]	77	M	Progressive thrombocytipenia	Bone marrow
Takahashi *et al*., 2020 [26]	75	F	Anemia	Stomach
Matsumoto *et al*., 2021 [53]	80	F	Loss of appetite Vomiting	Bone marrow
Ejaz *et al*., 2013 [71]	70	F	Pain in the left flank	Adrenal glands
Chen *et al*., 2021 [40]	36	M	Cauda equina syndrome	Peripheral nervous system
Kakutani *et al*., 2008 [52]	52	M	Dysuria Left lower extremity pain	Spinal canal and sacroiliac joint
Pujani *et al*., 2017 [41]	31	M	Chest pain Dry cough Weight loss	Mediastinum
Tang and Su, 2019 [51]	49	M	Low back pain	Bone
Cheng *et al*., 2021 [32]	42	F	Incidentally diagnosis	Liver
Ben Slama *et al*., 2017 [35]	55	F	Abdominal pain Jaundice Fever	Pancreas
Nakamura *et al*., 2023 [17]	80	M	Palpable lump	Lymph nodes of submandibular region
González-de Arriba *et al*., 2013 [72]	76	F	Skin nodules	Soft tissues
ShamaeiZadeh *et al*., 2024 [98]	71	F	Palpable lump	Inguinal lymp nodes
Shenoy *et al*., 2015 [73]	23	M	Fever Bone pain	Bone
El-Tani *et al*., 2016 [16]	58	F	Palpable lump	Breast
Dhandha *et al*., 2012 [74]	NA	F	Haematuria	Kidney Liver Soft tissues
Gaballa *et al*., 2020 [75]	76	M	Recurring pneumonia	Lung Cervical lymph nodes

Table 1. Continued.

Authors	Age of patients	Sex	Symptoms	MUP site
Christopoulos *et al*., 2012 [76]	34	M	Palpable lump	Cervical lymph nodes
Krishna Mohan *et al*., 2009 [100]	28	M	Abdominal pain	Stomach
			Anorexia	
			Weigh loss	
Matull *et al*., 2020 [77]	70	M	Painless palpable mass	Left deltoid muscle
Stagnitti *et al*., 2014 [12]	51	M	Abdominal pain	Small bowel
			Fever	
			Vomiting	
			No stool passage	
Tsaknis *et al*., 2021 [44]	57	M	Cough	Lung
Malafronte and Sorrells, 2009 [78]	36	M	Painless palpable mass	Axillary lymph nodes
Lewis *et al*., 2006 [79]	40	M	Painless palpable mass	Axillary lymph nodes
Tanaka *et al*., 2015 [80]	83	M	Abdominal pain	Liver
Averbukh *et al*., 2019 [24]	89	M	Dysphagia	Gastroesophageal junction
Hedayati *et al*., 2013 [81]	64	F	Dizziness	Small intestine
			Anemia	
			Abdominal pain	
			Weakness	
Pabianek *et al*., 2024 [82]	62	F	No symptoms	Subcutaneous tissue
Mondragón *et al*., 2019 [63]	36	F	Holocranial headache	Paraneoplastic presentation
			Opsoclonus-myoclonus syndrome	
Jiménez-Zarazúa *et al*., 2020 [99]	61	M	Ataxia	Paraneoplastic cerebellar presentation
			Vertigo	
			Dysarthria	
Sawalha and Alkilani, 2023 [38]	83	M	Mental confusion	Leptomeningeal
			Magnetic gait	
			Urinary incontinence	
Moorchung *et al*., 2004 [83]	22	F	Painless palpable lump	Axillary lymph nodes
Sethi and Raj, 2021 [84]	72	M	Painless palpable lump	Cervical lymph nodes
Gorris *et al*., 2021 [59]	59	M	Swelling	Salivary glands
Chantharasamee and Treetipsatit, 2018 [85]	51	F	Edema	Inguinal lymph nodes
			Painful left inguinal mass	
Singh *et al*., 2020 [86]	89	M	Weakness	Small intestine
			Weight loss	
			Gastrointestinal bleeding	
Agosto-Arroyo *et al*., 2017 [15]	28	F	Palpable mass	Breast
Wu *et al*., 2022 [28]	71	M	Fatigue	Small intestine
			Abdominal pain	
			Gastrointestinal bleeding	
Onozawa *et al*., 2014 [34]	58	F	Gallbladder bleeding	Gallbladder
Cho *et al*., 2009 [101]	56	F	Palpable mass	Axillary lymph nodes
Yan *et al*., 2023 [25]	66	F	Vomiting	Stomach
			Anorexia	
			Weight loss	
Vilar *et al*., 2024 [88]	47	M	Ileo-ileal intussusception	Small intestine
Verhulst *et al*., 2006 [89]	44	M	Scotoma	Macula
Dalal *et al*., 2013 [102]	60	M	Progressive vision loss	Ocular
Onan *et al*., 2010 [90]	31	F	Fatigue	Right atrium
			Weight loss	
Chew *et al*., 2021 [91]	40	F	Headache	Central nervous system
Patel *et al*., 2012 [92]	60	M	Vomiting	Small intestine
			Abdominal pain	
Navarrete-Dechent *et al*., 2021 [93]	70	F	Visual loss	Paraneoplastic syndrome (B-DUMP)
Fabiani *et al*., 2016 [50]	78	M	Palpable prostatic mass	Seminal vescicle
Papoutsoglou *et al*., 2013 [94]	40	M	Hypospermia	Seminal vescicle

Table 1. Continued.

Authors	Age of patients	Sex	Symptoms	MUP site
Rapisuwon *et al*., 2016 [95]	67	F	Dyspnea	Bone marrow
			Weight loss	
Deng *et al*., 2024 [96]	51	F	Palpable mass	Inguinal lymph nodes
Doyle *et al*., 2023 [18]	78	M	Palpable mass	Skin metastases
	64	M	Headache	Brain
	45	F	Palpable mass	Lymph nodes
	59	M	Palpable mass	Lymph nodes
	84	F	Palpable mass	Lymph nodes
	50	F	Palpable mass	Lymph nodes
Eltawansy *et al*., 2015 [21]	58	M	Painful palpable mass	Inguinal lymph nodes
Babu *et al*., 2022 [22]	73	F	Subcutaneous swellings	Soft tissue
Sirvan *et al*., 2019 [23]	52	M	Vomiting	Small intestine
			Loss of weight	
			Abdominal pain	
	29	M	Subcutaneous swellings	Soft tissue
	49	F	Palpable mass	Soft tissue
	46	M	Hypertrophic lesion	Soft tissue
Spoto *et al*., 2018 [64]	43	F	Painful subcutaneous nodules	Soft tissue
Liu *et al*., 2024 [65]	52	M	Subcutaneous mass	Soft tissue
Myrou *et al*., 2021 [66]	73	M	Vomiting	Stomach
			Anorexia	
			Nausea	
Vrable and Chang, 2017 [27]	51	F	Bowel obstrucion	Small intestine
Reddy *et al*., 2014 [29]	73	M	Subcutaneous mass	Parotid gland
Mui and Pham, 2019 [10]	36	F	Vomiting	Small intestine
			Abdominal pain	
			Constipation	
De Monti *et al*., 2018 [11]	69	NA	Vomiting	Small intestine
			Abdominal pain	
Wang *et al*., 2023 [31]	65	M	Anorexia	Liver
			Nausea	
			Vomiting	
Tiong *et al*., 2023 [33]	50	F	NA	Liver
Kuriakose *et al*., 2015 [42]	54	M	Dyspnea	Right atrial
			Lower extremity edema	
Garcia-Ramiu *et al*., 2022 [37]	35	F	Ataxia	Brain
			Nausea	Placenta
			Vomiting	
			Headache	
			Diplopia	
Mremi *et al*., 2021 [13]	43	F	Headache	Brain
Naing *et al*., 2004 [39]	42	F	Numbness	Mass in L2
El Haj *et al*., 2021 [43]	45	F	Chest pain	Lung
Gebauer *et al*., 2020 [45]	54	F	Ptosis	Lung
			Chest pain	
Azoury *et al*., 2015 [46]	74	F	Epistaxis	Nasopharyngeal
Diamantopoulos *et al*., 2023 [48]	47	M	Melanuria	Genitourinary tract
Meng and Werboff, 2000 [49]	33	M	Hematospermia	Genitourinary tract
Rastrelli *et al*., 2014 [58]	30	F	Antalgic flexion of the hand	Muscles
Blanco *et al*., 2014 [61]	80	M	Asthenia	Adrenal glands
			Weight loss	
Drouet *et al*., 2017 [60]	51	M	Asthenia	Adrenal glands
			Weight loss	
			Dorsal pain	
Ontiveros Ramírez *et al*., 2025 [97]	74	F	Abdominal pain	Small bowel

MUP, melanoma of unknown primary origin; M, male; F, female. NA, not applicable; B-DUMP, bronchial-diabetes urolithiasis myopathy polyneuropathy; T6, 6th thoracic vertebra; T7, 7th thoracic vertebra; L2, 2nd lumbar vertebra.

Table 3 (Ref. [9–102]) provides an overview of therapeutic approaches and follow-up data extracted from the case reports included in our review. A wide heterogeneity in treatment strategies was observed, reflecting variability in clinical presentation, disease stage, and treatment availability. Surgery was the most commonly adopted initial approach, particularly in cases presenting with isolated nodal or visceral metastases. This mainly included

Table 2. Characteristics of reports included. Male/female sex involvement; nodes, subcutaneous tissues and visceral organ involvement.

Characteristic	Number (n)/description
Male/female sex	52/37
Lymph nodes involvement	16 (axillary 6; cervical 5; inguinal 4; others 1)
Soft tissues involvement	7
Gastrointestinal tract involvement	16 (gastric 6; small bowel 10)
Nervous system involvement	11 (brain 6; spinal cord 5)
Bones/muscles involvement	6/5
Liver involvement	8
Respiratory tract involvement	7
Mediastinum/heart involvement	3
Pancreas/gallbladder involvement	2/1
Genitourinary tract involvement	5
Glands involvement	Adrenal glands 3; salivary glands 1
Breast involvement	2
Paraneoplastic involvement	2

lymph node dissections (axillary, inguinal, cervical) and emergency resections for symptomatic visceral involvement (e.g., bowel obstruction, hemorrhage). Immunotherapy has been widely employed, especially in recent years, with agents such as Nivolumab, Ipilimumab, and Pembrolizumab. Targeted therapies were used in patients with brain-derived neurotrophic factor-related serine/threonine-protein kinase (*BRAF*) mutations, with dabrafenib + trametinib or vemurafenib, either as neoadjuvant or adjuvant treatment. Chemotherapy (e.g., dacarbazine, temozolomide, FOLFIRINOX) was reported in selected cases, though less frequently in the modern immunotherapy era. Adjuvant or palliative radiotherapy was administered in multiple cases, either following surgery (especially for nodal basins or central nervous system (CNS) metastases) or as a sole therapy in inoperable patients. Modalities of radiotherapy included external beam radiation, brachytherapy, and stereotactic brain radiotherapy.

Discussion

MUP Diagnosis and Pathogenesis

The first definition of MUP was proposed in 1963 by DASGUPTA *et al*. [3]. DASGUPTA originally defined four exclusion criteria for MUP:

(1) Evidence of previous orbital exenteration or enucleation;
(2) Evidence of previous skin excision, electrodesication, cauterization, or other surgical manipulation of skin;
(3) Evidence of metastatic melanoma in a draining lymph node with a scar on the skin overlying that lymph node basin;
(4) Lack of a thorough physical examination, including the absence of an ophthalmologic, anal and genital exam.

If any of these criteria are met, patients should be categorized as having a melanoma of known primary origin (MKP) rather than MUP. Thus, according to DASGUPTA criteria, a thorough evaluation, including ophthalmologic and anogenital examinations, is required when melanoma is diagnosed within the subcutaneous tissue, lymph nodes (LNs), or visceral organs without an obvious primary source. Despite DASGUPTA's criteria, a study conducted in Denmark recommends evaluating the patient's past medical history, a complete skin examination and total body CT/positron emission tomography (PET) scans for staging purposes. The study concluded that screening to detect the primary tumor site is both costly and redundant, and that only rarely does this search lead to the identification of a primary skin tumor.

The exact pathogenesis of MUP remains unclear, although several hypotheses have been proposed. The most widely supported theory is the spontaneous regression of a primary cutaneous melanoma, mediated by the host immune system. This concept was first introduced by Smith and Stehlin in 1965 [6] and is supported by both clinical and molecular findings.

Histopathological analyses of regressed melanomas often reveal dense infiltrates of cytotoxic T lymphocytes, fibrosis, and melanophages, features consistent with an immune-mediated elimination of tumor cells. Recent immunohistochemical and transcriptomic studies have identified several key immune characteristics in MUP tumors, including an increased infiltration of cluster of differentiation 8 ($CD8^+$) T lymphocytes and natural killer (NK) cells, overexpression of major histocompatibility complex (MHC) class I and II molecules, which enhance antigen presentation, upregulation of interferon-stimulated genes (ISGs) and immune-related chemokines such as C-X-C Motif Chemokine Lig-

Table 3. Therapies and follow-up data reported in the included case reports.

Study (author, year)	Therapy adopted	Follow-up
Cortellini *et al*., 2021 [9]	N.R.	N.R.
Mui and Pham, 2019 [10]	Emergency right hemicolectomy	N.R.
De Monti *et al*., 2018 [11]	Emergency surgery	44 months, disease-free
Stagnitti *et al*., 2014 [12]	Small bowel resection + axillary lymph nodes dissection adjuvant CT	8 weeks, death
Mremi *et al*., 2021 [13]	Excision biopsy	N.R.
Takagi *et al*., 2020 [14]	Laminectomy Adjuvant RT	12 months, death
Agosto-Arroyo *et al*., 2017 [15]	Nivolumab + ipilimumab, then dabrafenib + tramatenib	8 months, death
El-Tani *et al*., 2016 [16]	Mastectomy + axillary lymph nodes dissection Adjuvant RT	Progression with brain metastasis; F.U.: N.R.
Nakamura *et al*., 2023 [17]	RT	76 months, no metastasis or progression of disease
Doyle *et al*., 2023 [18]	Immunotherapy	60 months, no metastasis or progression of disease
Phan *et al*., 2021 [19]	Dabrafenib + trametinib then axillary lymph node dissection	F.U. duration: N.R.
Bankar *et al*., 2015 [20]	Axillary lymph nodes dissection and wedge resection of stomach mass	Disease-free 6 months, disease-free
Eltawansy *et al*., 2015 [21]	Inguinal lymph-nodes dissection Adjuvant RT + ipilimumab	N.R.
Babu *et al*., 2022 [22]	N.R.	N.R.
Sirvan *et al*., 2019 [23]	(1) Temodal treatment+ inguinal lymph node dissection. (2) Interleukin (3) Vemurafenib (4) Surgical excision	(1) 60 months, death (2) Disease-free; F.U. duration: N.R. (3) Disease-free; F.U. duration: N.R. (4) N.R.
Averbukh *et al*., 2019 [24]	Application of percutaneous endoscopic gastrostomy tube	N.R.
Yan *et al*., 2023 [25]	Ipilimumab + nivolumab	2 months, death
Takahashi *et al*., 2020 [26]	Total gastrectomy	120 months, disease-free
Vrable and Chang, 2017 [27]	Emergency small bowel resection Adjuvant IFN-alfa	12 months, no metastasis or progression of disease
Wu *et al*., 2022 [28]	Small-bowel resection Palliative immunotherapy	N.R.
Reddy *et al*., 2014 [29]	Left total parotidectomy and cervical lymph node dissection Adjuvant RT Laparoscopic resection of his sigmoid colon and right adrenalectomy	Recurrence of disease at level of buccal space 2 months after diagnosis; recurrence of disease at level of sigma and right adrenal gland 7 months after diagnosis Disease-free; duration F.U.: N.R.
Yuan *et al*., 2023 [30]	Pembrolizumab	60 months, disease free
Wang *et al*., 2023 [31]	N.R.	N.R.
Cheng *et al*., 2021 [32]	BRAF and MEK inhibitors, then nivolumab+ ipililumab	9 months, death
Tiong *et al*., 2023 [33]	Pembrolizumab, then ipililumab	5 months, alive
Onozawa *et al*., 2014 [34]	Laparoscopic cholecystectomy Adjuvant DAC-Tam chemotherapy + CVD chemotherapy	8 months, death
Ben Slama *et al*., 2017 [35]	Pancreaticoduodenectomy	9 months, death
Nguyen *et al*., 2022 [36]	Brain RT+ BRAF-inhibitors	N.R.
Garcia-Ramiu *et al*., 2022 [37]	Craniotomy and resection of the brain lesion Adjuvant RT, nivolumab and ipililumab	Disease free; duration of F.U: N.R.
Sawalha and Alkilani, 2023 [38]	Placement of lumbar drain Hospice care	N.R.

Table 3. Continued.

Study (author, year)	Therapy adopted	Follow-up
Naing *et al*., 2004 [39]	Surgery Adjuvant RT and IFN-alfa	Disease free; duration of F.U: N.R.
Chen *et al*., 2021 [40]	RT	N.R.
Pujani *et al*., 2017 [41]	CT+ immunotherapy	1 month, death
Kuriakose *et al*., 2015 [42]	Surgery Ipililumab + pembrolizumab	Progression into the peritoneal cavity; duration of F.U: N.R.
El Haj *et al*., 2021 [43]	Surgery Adjuvant Nivolumab	Disease-free; duration of F.U: N.R.
Tsaknis *et al*., 2021 [44]	Surgery Adjuvant dabrafenib and trametinib	Disease-free; F.U.: 5 years
Gebauer *et al*., 2020 [45]	Neoadjuvant vemurafenib Surgery	Disease-free; F.U.: 6 years
Azoury *et al*., 2015 [46]	Neoadjuvant IL-2 Hepatic perfusion	Disease-free; F.U.: 7 years
Kim *et al*., 2023 [47]	Surgery, adjuvant RT Lobectomy and mediastinal lymphadenctomy Adjuvant pembrolizumab	F.U.: 9 months, lung and brain metastasis
Diamantopoulos *et al*., 2023 [48]	BRAF and MEK inhibitors	Death, duration of F.U: N.R.
Meng and Werboff, 2000 [49]	RT + IFN-alfa	F.U.: 5 months, death
Fabiani *et al*., 2016 [50]	Surgery	N.R.
Tang and Su, 2019 [51]	Laminectomy	F.U.: 5 months, metastasis in head and sternum
Kakutani *et al*., 2008 [52]	Radiotherapy + chemotherapy (DAC-Tam)	F.U.: 9 months, death
Matsumoto *et al*., 2021 [53]	No therapy	F.U.: 9 months, death
Suzuki *et al*., 2014 [54]	No therapy	Death after 1 week
Andrianandrasana *et al*., 2023 [55]	RT + decarbazine	Disease-free; duration of F.U: N.R.
Grech *et al*., 2020 [56]	Surgery Adjuvant nivolumab	Progression with liver metastasis; duration of F.U: N.R.
Dalle Carbonare *et al*., 2017 [57]	Surgery	Disease free; F.U: 3 months
Rastrelli *et al*., 2014 [58]	Neoadjuvant dabrafenib Surgery Adjuvant RT+ IFN-alfa	F.U. 7 months, disease free
Gorris *et al*., 2021 [59]	Surgery Adjuvant nivolumab	F.U.: 12 months, disease-free
Drouet *et al*., 2017 [60]	Surgery	F.U.: 48 months, disease-free
Blanco *et al*., 2014 [61]	N.R.	N.R.
Rieth *et al*., 2021 [62]	RT + pembrolizumab	F.U.: 6 months, death
Mondragón *et al*., 2019 [63]	No therapy	Death after 13 days
Spoto *et al*., 2018 [64]	Surgery	N.R.
Liu *et al*., 2024 [65]	Axillary lymph node dissection Adjuvant target therapy Resection of the para-renal mass and adrenal metastasis	F.U. 20 months, disease free
Myrou *et al*., 2021 [66]	N.R.	N.R.
Jin *et al*., 2020 [67]	Surgery Adjuvant IFN-alfa	F.U.: 20 months, disease-free
Rice-Canetto *et al*., 2024 [68]	Surgery Adjuvant RT	F.U.: 20 months, disease-free
Proboka *et al*., 2018 [69]	Surgery Adjuvant RT	F.U.: 12 months, disease-free
Shan *et al*., 2009 [70]	Palliative therapy	F.U.: 1 month, death
Ejaz *et al*., 2013 [71]	RT + CT (temozolomide)	F.U.: 6 months, death
González-de Arriba *et al*., 2013 [72]	Surgery	F.U.: 96 months, disease-free
Shenoy *et al*., 2015 [73]	N.R.	N.R.

Table 3. Continued.

Study (author, year)	Therapy adopted	Follow-up
Dhandha *et al*., 2012 [74]	Ipililumab	Death, duration of F.U: N.R.
Gaballa *et al*., 2020 [75]	Ipililumab, nivolumab	F.U.: 12 months, disease-free
Christopoulos *et al*., 2012 [76]	Surgery Adjuvant CT	F.U.: 48 months, disease-free
Matull *et al*., 2020 [77]	Ipililumab + nivolumab RANK-L inhibitor denosumab + infliximab	F.U.: 48 months, disease-free
Malafronte and Sorrells, 2009 [78]	Axillary lymph node dissection	N.R.
Lewis *et al*., 2006 [79]	Surgery	N.R.
Tanaka *et al*., 2015 [80]	N.R.	F.U.: 47 days, death
Hedayati *et al*., 2013 [81]	Emergency small bowel resection Adjuvant dacarbazine	F.U.: hospice care, duration of F.U: N.R.
Pabianek *et al*., 2024 [82]	Surgery Adjuvant nivolumab	N.R.
Moorchung *et al*., 2004 [83]	CT	F.U.: 3 months, death
Sethi and Raj, 2021 [84]	FOLFIRINOX Pembrolizumab	N.R.
Chantharasamee and Treetipsatit, 2018 [85]	RT CT with carboplatin and paclitaxel	F.U.: 60 months, disease-free
Singh *et al*., 2020 [86]	Emergency small bowel resection	F.U.: 9 months, recurrence of disease
Bordeanu-Diaconescu *et al*., 2024 [87]	Local debridement, drainage, and excisional biopsy	N.R.
Vilar *et al*., 2024 [88]	Emergency small bowel resection	F.U.: 14 days, death
Verhulst *et al*., 2006 [89]	CT + RT	F.U.: 7 months, death
Onan *et al*., 2010 [90]	Surgery Adjuvant CT	F.U.: 12 months, disease-free
Chew *et al*., 2021 [91]	RT + ipililumab and nivolumab Dacarbazine Pembrolizumab Trametinib	F.U.: 48 months, death
Patel *et al*., 2012 [92]	Emergency small bowel resection	F.U.: 6 months, no other information
Navarrete-Dechent *et al*., 2021 [93]	N.R.	N.R.
Papoutsoglou *et al*., 2013 [94]	CT	F.U.: 6 months, death
Rapisuwon *et al*., 2016 [95]	Dabrafenib with trametinib	F.U.: 32 weeks, disease-free
Deng *et al*., 2024 [96]	Surgery Adjuvant teraplizumab and temozolomide Dabrafenib and trametinib Paclitaxel, carboplatin and bevacizumab RT, pembrolizumab and dacarbazine, brachytherapy	F.U.: 36 months, death
Ontiveros Ramírez *et al*., 2025 [97]	Emergency small bowel resection	N.R.
ShamaeiZadeh *et al*., 2024 [98]	Nivolumab	F.U.: 12 months, disease-free
Jiménez-Zarazúa *et al*., 2020 [99]	Dabrafenib and trametinib	N.R.
Krishna Mohan *et al*., 2009 [100]	Temozolamide	Death; duration of F.U: N.R.
Cho *et al*., 2009 [101]	RT, IFN-alfa, dacarbazine and narrow band UVB phototherapy	Disease-free; duration of F.U.: N.R.
Dalal *et al*., 2013 [102]	N.R.	N.R.

N.R., not reported; F.U., follow-up; RT, radiotherapy; DAC-Tam, Dacarbazine, ACNU (Nimustine), Cisplatin, and Tamoxifen; CVD, Cyclophosphamide, Vincristine, and Dacarbazine; IFN, interferon; *BRAF*, brain-derived neurotrophic factor-related serine/threonine-protein kinase; IL-2, interleukin-2; RANK-L, receptor activator of nuclear factor kappa-B ligand; UVB, ultraviolet radiation B; MEK, mitogen-activated protein kinase kinase.

and (CXCL)9 and CXCL10 and elevated expression of programmed death-ligand 1 (PD-L1) [103–106].

These findings indicate that MUP tumors may represent an immunologically active phenotype, potentially explaining the enhanced clinical response to immune checkpoint inhibitors observed in some patients.

Moreover, MUP tumors often exhibit a high tumor mutational burden (TMB), leading to the production of numer-

ous neoantigens capable of eliciting a strong adaptive immune response. This molecular signature may account for both the immune-mediated regression of the primary tumor and the increased responsiveness to immunotherapy.

Despite strong support for the immune regression hypothesis, two alternative mechanisms remain biologically plausible: the presence of an undetected or misdiagnosed primary melanoma, potentially located in anatomically obscure sites such as the mucosa, ocular structures, or subungual regions and the malignant transformation of ectopic melanocytes (e.g., within lymph nodes or visceral tissues) under oncogenic stimuli such as *BRAF* or neuroblastoma rat sarcoma (RAS) viral oncogene homolog (*NRAS*) mutations.

MUP Staging and Symptoms

There is still no unanimous agreement regarding the staging of patients with MUP. In fact, previously patients with subcutaneous tissue and/or lymph node metastatic melanoma, without a detectable primary tumor, were categorized as stage III B or IIIC disease; by contrast, patients presenting with distant metastases, including visceral metastases, were categorized as stage IV disease [7,107]. According to the 8th Edition of the American Joint Committee on Cancer (AJCC) staging criteria, however, patients with MUP should always be assigned a T0 and classified as stage IV disease [108,109].

Lymph nodes are the most common site of MUP: in men, axillary and cervical lymph nodes are predominantly affected, while in women, inguinal lymph node involvement is more frequent. In most of the studies included in our review, patients with nodal MUP presented with a palpable and painless lump.

Regarding extra-nodal involvement, subcutaneous tissues and gastrointestinal tract are among the most frequently affected sites, followed by other visceral organs. Patients with subcutaneous tissues MUPs can be affected by hyperpigmented skin lesions, with or without ulceration, or by skin-colored swelling. According to our review, one of the most common visceral sites affected by MUP is the gastrointestinal (GI) tract. Nine of the studies included reported involvement of the small bowel: intestinal MUP can present as an emergency with hemorrhage, small bowel obstruction and intussusception or in a non-emergency setting with vomiting, nausea, abdominal pain and weight loss. Seven studies, instead, described gastric MUPs: in most of these cases, it presented as a polypoid lesion. Symptoms such as nausea, vomiting or weight loss may also occur in cases of liver involvement: eight of the studies included in our review described liver MUPs and authors referred these symptoms except for Tiong *et al*. [33], who described an acute presentation due to hepatic rupture.

Brain involvement is also described: clinical presentation is variable, depending on the involved cerebral area. In most cases, patients present with headache, dizziness, diplopia or nausea and vomiting. One of the most common cortical areas affected by MUP is the frontal lobe whose involvement is associated with psychiatric symptoms. Spinal involvement, although rare, was described in only five reports. Symptoms range from numbness to cauda equina syndrome.

Seven studies reported respiratory tract MUPs: typically, patients with endobronchial MUPs are affected by cough and hemoptysis, while the nasopharyngeal MUP can cause chronic epistaxis.

Another possible site of MUP is the bones. While MUP can affect any bone, spinal vertebrae are the most frequently affected site, with clinical manifestations similar to spinal root compression, often accompanied by pathological fractures.

Only a few articles described MUPs of the pancreas, gallbladder and genitourinary tract. Symptoms are described in Table 1 in the Results section.

MUP Prognosis and Treatment

Several studies have evaluated the prognosis of patients with MUP compared to those with MKP melanoma at similar disease stages. Some retrospective analyses and prospective trials, such as those by Lee *et al*. [4], Bae *et al*. [110], and van der Ploeg *et al*. [111], have reported a more favorable prognosis in patients with MUP. This improved outcome has been hypothesized to result from heightened immune-mediated tumor surveillance and regression.

Supporting this theory, a large dataset from the E1609 adjuvant immunotherapy trial demonstrated that MUP patients experienced significantly improved relapse-free survival (RFS) and overall survival (OS), suggesting increased sensitivity to immune checkpoint inhibitors (ICIs) in this subgroup [112].

Conversely, other studies [113,114] have reported worse clinical outcomes in MUP patients, highlighting a lack of consensus in the literature. These conflicting results may be influenced by lead-time bias, tumor heterogeneity, and the distinct biological characteristics of MUP tumors.

Recent investigations have aimed to clarify these discrepancies by exploring molecular and immunological correlates. Transcriptomic analyses have revealed that MUP tumors are often enriched in immune-related gene expression, with increased infiltration of $CD4^+$ and $CD8^+$ T cells, natural killer (NK) cells, and B cells. These immune microenvironment features suggest a more immunogenic tumor phenotype, potentially translating into improved prognosis and responsiveness to ICIs [115].

Moreover, MUP tumors frequently exhibit a high tumor mutational burden (TMB), which is associated with the generation of neoantigens and a “hot” immune microenvironment. In this context, increased expression of interferon (IFN)-γ and chemokines such as CXCL9 and CXCL10 correlates with enhanced immune activation and better survival outcomes [107].

Despite shared mutational landscapes between MUP and MKP, particularly involving *BRAF*, *NRAS*, and KIT proto-oncogene, receptor tyrosine kinase (*KIT*), recent evidence suggests that telomerase reverse transcriptase (TERT) promoter mutations are more prevalent in MUP and may be associated with poorer overall survival [116].

In conclusion, while some data support a favorable prognosis in MUP due to its immunogenic profile, results across studies remain inconclusive. Immune profiling, including tumor-infiltrating lymphocyte (TIL) density, MHC class I/II expression, and immune gene signatures, appears to be critical in identifying MUP patients who are most likely to benefit from ICI therapy. Integrative approaches involving multiplex immunohistochemistry, single-cell RNA sequencing, and immune-related transcriptomic profiling (e.g., IFN-γ, CXCL9/10, immunologic constant of rejection (ICR) score) are strongly recommended [117].

Additionally, TERT promoter status and oncogenic mutations (e.g., *BRAF*, *NRAS*) should be evaluated as potential prognostic and predictive biomarkers. Given the unique clinical and biological features of MUP, future prospective trials incorporating immune and mutational profiling are essential to personalize therapeutic strategies and better define prognosis in this rare melanoma subset.

Although no specific guidelines exist for MUP, the American Society of Clinical Oncology (ASCO) [118] suggests that current management for MUP should mirror that of cytoplasmic mitogen-activated protein kinase phosphatases (cMKP) at the same stage, incorporating surgical resection, regional nodal dissection, adjuvant and neoadjuvant immune checkpoint inhibitors, and, when indicated, radiotherapy. We performed a review of the literature, and we found numerous studies [119–121] suggesting that patients with MUP should be treated early with a management approach similar to that offered to cMKP patients. Our review reveals a trend toward increasing use of immune checkpoint inhibitors and targeted agents, reflecting evolving standards of care. Nevertheless, surgical excision remains central in the management of resectable MUP lesions. The data support a multidisciplinary approach, often tailored to individual disease patterns and molecular profiles. Surgery can improve overall patient survival: it may include lymphadenectomy, craniotomy, lung resection and bowel resection or other possible surgical approaches depending on the location of metastases. It can be performed for curative purposes, but also for palliative purposes or in emergency settings to reduce acute symptoms. Thus, the absence of a primary site should not preclude surgical management. However, these patients should be considered for adjuvant therapies similar to those aimed at stage IV cMKP patients. Nowadays, novel therapies have been implemented. Since 2011 several systemic therapies have been approved including immune checkpoint inhibitors and targeted therapies (BRAF and mitogen-activated protein kinase kinase (MEK) inhibitors). Immunotherapy includes monoclonal antibodies, such as Ipilimumab, Nivolumab or Pembrolizumab, that suppress anti-tumoral T cell activity. Ipilimumab is the first monoclonal antibody approved and used for the treatment of metastatic melanoma: it is an immune checkpoint inhibitor targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4). In contrast, Nivolumab and Pembrolizumab are monoclonal antibodies approved in 2015, and they are programmed cell death protein 1 (PD-1) blocking antibodies. Targeted therapies operate in a different way, inhibiting tumour cell proliferation. Targeted therapy includes BRAF inhibitors, such as vemurafenib, dabrafenib and encorafenib, and MEK inhibitors, including trametinib. While immunotherapy is available for every patient, the use of targeted therapy depends on the mutation status of the *BRAF* gene.

In the era of novel therapies, the treatment of patients with MUP has changed: a recent study, published in April 2023 and conducted by Rousset *et al*. [122], showed that patients with MUP benefited from novel therapies as much as those with cMKP. In fact, in the pre-novel therapy era, the median OS of stage III MUP ranged from 24 to 127 months, while the OS of patients with stage IV MUP was significantly shorter, ranging between 3 and 13 months [123]. Nowadays, in the post-novel therapy era, the impact of immunotherapy and targeted therapies on MUP is similar to that in cMKP patients. A study, conducted by Gambichler *et al*. [124] evaluated the outcomes of novel therapies in MUP patients, comparing the results to those reported for cMKP. The results demonstrated an objective response in both groups and similar findings were obtained by an observational study, conducted in 2020 by Verver *et al*. [125]. In addition, Verver *et al*. [125] showed that patients with stage IV MUP experienced a significantly improved OS when novel therapies were included in the clinical treatment.

Limitations

This review is based only on case reports and case series, which inherently present several limitations. First, the inclusion of only case reports introduces a significant publication bias, as unusual or successful cases are more likely to be reported, whereas negative or inconclusive outcomes may be underrepresented. Consequently, the collected data may not fully reflect the broader clinical spectrum of melanoma of unknown primary origin. Second, heterogeneity in clinical details and reporting standards among case reports can hinder the ability to draw consistent and generalizable conclusions. Important variables such as staging methodology, follow-up duration, immunohistochemical analyses, and therapeutic rationale are often inconsistently described or omitted altogether. Third, the retrospective and descriptive nature of case reports limits the ability to assess causality or compare the efficacy of different diagnostic and therapeutic strategies. This makes it difficult to perform any form of statistical aggregation or meta-analysis, further constraining the strength of the evi-

dence. Finally, selection bias may affect the representativeness of the data. Cases with better prognosis or unexpected presentations are more likely to be published, potentially overestimating the frequency of certain findings or the success of treatments.

Despite these limitations, the aggregation of case reports remains valuable, particularly for rare entities such as MUP, where large-scale prospective data are lacking. This review offers an overview of clinical patterns and management approaches that may serve as a foundation for future studies or guideline development.

Conclusions

The exact pathogenesis of MUP is still unknown. According to the 8th Edition of the American Joint Committee on Cancer, patients with melanoma of unknown primary origin should always be classified as stage IV. Treatment depends on the location of melanoma metastases. However, it is generally similar to the treatment for patients with MKP: MUP cases should be managed according to strategies similar to those used for stage IV. Both forms of melanoma benefit from treatment with novel therapies. All patients should be managed in highly specialized centers and their cases should be discussed in multidisciplinary meetings (MDMs).

Availability of Data and Materials

All data related to regarding this case report are included in the manuscript.

Author Contributions

Conceptualization: MM, RC and VDA; methodology and investigation: MM, MCR, LP, AR and SG; data analysis: MM, SG, BC, AP, PB and RC; writing, original draft preparation: MM, SG, RC, LP and VDA. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The studies involving humans were approved by the Review Board of the Italian Society of Research in Surgery (n. 0030/2025). The study was conducted in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the patient for the publication of this case report and accompanying images. The investigations were conducted in accordance with the principles outlined in the Declaration of Helsinki.

Acknowledgment

We thank Prof. Renzo Mocini, Associate Prof. of English and Translation at the Department of Surgery, Sapienza of Rome, who contributed to the the review of the manuscript.

Funding

This research received no external funding.

Conflict of Interest

Roberto Cirocchi is a member of the editorial board and guest editor of this journal. We declare that Roberto Cirocchi had no involvement in the peer review of this article and has no access to information regarding its peer review. Other authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.4214.

References

[1] Cirocchi R, Cicoletti M, Arcangeli F, Tebala GD, Bruzzone P, Avenia S, *et al*. Preliminary Study of Axillary Lymphatic Drainage in Cutaneous Melanoma Patients: A Cross-Sectional Study. Medicina (Kaunas, Lithuania). 2023; 59: 1357. https://doi.org/10.3390/medicina59081357.

[2] AIOM. *Linee Guida AIOM per il Trattamento del Melanoma*. Associazione Italiana di Oncologia Medica: Milan, Italy. 2023. Available at: https://www.aiom.it/linee-guida-aiom/ (Accessed: 21 May 2025).

[3] DASGUPTA T, BOWDEN L, BERG JW. MALIGNANT MELANOMA OF UNKNOWN PRIMARY ORIGIN. Surgery, Gy-necology & Obstetrics. 1963; 117: 341–345.

[4] Lee CC, Faries MB, Wanek LA, Morton DL. Improved survival after lymphadenectomy for nodal metastasis from an unknown primary melanoma. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2008; 26: 535–541. https://doi.org/10.1200/JCO.2007.14.0285.

[5] Kamposioras K, Pentheroudakis G, Pectasides D, Pavlidis N. Malignant melanoma of unknown primary site. To make the long story short. A systematic review of the literature. Critical Reviews in Oncology/hematology. 2011; 78: 112–126. https://doi.org/10.1016/j.critrevonc.2010.04.007.

[6] Smith JL, Jr, Stehlin JS, Jr. Spontaneous regression of primary malignant melanomas with regional metastases. Cancer. 1965; 18: 1399–1415. https://doi.org/10.1002/1097-0142(196511)18:11<1399::aid-cncr2820181104>3.0.co;2-r.

[7] Menzies SW, McCarthy WH. Complete regression of primary cutaneous malignant melanoma. Archives of Surgery (Chicago, Ill.: 1960). 1997; 132: 553–556. https://doi.org/10.1001/archsurg.1997.01430290099020.

[8] Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D, *et al*. The CARE guidelines: consensus-based clinical case report guideline development. Journal of Clinical Epidemiology. 2014; 67: 46–51. https://doi.org/10.1016/j.jclinepi.2013.08.003.

[9] Cortellini F, Marasco G, Renzulli M, Vasuri F, Ricciardiello L. Gastric Melanoma of Unknown Primary. Journal of Gastrointesti-nal and Liver Diseases: JGLD. 2021; 30: 14. https://doi.org/10.15403/jgld-3420.

[10] Mui M, Pham T. Ileocaecal intussusception due to melanoma from an

unknown primary. ANZ Journal of Surgery. 2019; 89: E584–E585. https://doi.org/10.1111/ans.15003.

[11] De Monti M, Pacchiarini L, Cestaro G, Peloni G, Fasolini F. Small bowel intussusception due to malignant melanoma: primary lesion or metastases? A case report. Il Giornale Di Chirurgia. 2018; 39: 184–187.

[12] Stagnitti F, Orsini S, Martellucci A, Tudisco A, Avallone M, Aiuti F, *et al*. Small bowel intussussception due to metastatic melanoma of unknown primary site. Case report. Il Giornale Di Chirurgia. 2014; 35: 246–249.

[13] Mremi A, Goodluck G, Sadiq A, Lodhia J. Metastatic malignant melanoma of unknown primary site to the brain: A case report. International Journal of Surgery Case Reports. 2021; 86: 106311. https://doi.org/10.1016/j.ijscr.2021.106311.

[14] Takagi Y, Yamada H, Ebara H, Hayashi H, Kidani S, Okamoto S, *et al*. Thoracic extradural malignant melanoma with unknown primary. BJR Case Reports. 2020; 6: 20200042. https://doi.org/10.1259/bjrcr.20200042.

[15] Agosto-Arroyo E, Rosa M, Chau A, Khazai L. Concurrent *BRAF* and *PTEN* mutations in melanoma of un-known origin presenting as a breast mass. SAGE Open Medical Case Reports. 2017; 5: 2050313X17711064. https://doi.org/10.1177/2050313X17711064.

[16] El-Tani Z, Duc C, Gluecker T, Cottier O. Intramammary metastatic melanoma of unknown primary origin in a 58-year old patient: a case report. Journal of Medical Case Reports. 2016; 10: 363. https://doi.org/10.1186/s13256-016-1117-y.

[17] Nakamura M, Ohnishi K, Uchida F, Saito T, Kitagawa Y, Matsuoka R, *et al*. Proton beam therapy for cervical lymph node metastasis in an octogenarian with melanoma of unknown primary: a case report. International Cancer Conference Journal. 2023; 12: 160–165. https://doi.org/10.1007/s13691-023-00597-8.

[18] Doyle C, O'Sullivan B, Watchorn RE, Eustace K. Melanoma of unknown primary: a case series. Irish Journal of Medical Science. 2023; 192: 65–66. https://doi.org/10.1007/s11845-022-02951-w.

[19] Phan MB, Phan J, Nguyen C, He J, Nguyen QD. Melanoma With an Unknown Primary in an Asymptomatic Elderly Male With Unilateral Lymphadenopathy. Cureus. 2021; 13: e15140. https://doi.org/10.7759/cureus.15140.

[20] Bankar S, Patkar S, Desai S, Shrikhande SV. Unusual presentation of melanoma of unknown primary origin: A case report and review of literature. Journal of Cancer Research and Therapeutics. 2015; 11: 1025. https://doi.org/10.4103/0973-1482.148680.

[21] Eltawansy SA, Panasiti R, Hasanien S, Lourdusamy D, Sharon D. Metastatic malignant melanoma of the inguinal lymph node with unknown primary lesion. Case Reports in Medicine. 2015; 2015: 879460. https://doi.org/10.1155/2015/879460.

[22] Babu AK, Mizaj Z, Gowda V, Jaleel A, John NM, Nair Santhamma SG, *et al*. Metastatic Melanoma with an Unknown Primary. Indian Journal of Dermatology. 2022; 67: 627. https://doi.org/10.4103/ijd.ijd_256_22.

[23] Sirvan SS, İhsan Eren H, Kurt Yazar S, Günenç AC, Yeşilada AK, Irmak F, *et al*. Approach to Patients with Malignant Melanoma of Unknown Primary Origin. Sisli Etfal Hastanesi Tip Bulteni. 2019; 53: 125–131. https://doi.org/10.14744/SEMB.2019.52333.

[24] Averbukh LD, Mavilia MG, Aujla AK. Secondary Gastrointestinal Melanoma of Unknown Origin: A Case Report of a Rare En-tity. Cureus. 2019; 11: e4720. https://doi.org/10.7759/cureus.4720.

[25] Yan ZH, Huang J, Chiang J, Kwan KWC. Metastatic Gastric Mucosal Melanoma: A Rare Case Presenting With Diffuse Gastric Polyposis. Cureus. 2023; 15: e43740. https://doi.org/10.7759/cureus.43740.

[26] Takahashi T, Sugita S, Kagaya H, Morita T. Surgically treated gastric melanoma of unknown primary: A case report from a 10-year survivor. Pathology International. 2020; 70: 786–792. https://doi.org/10.1111/pin.12991.

[27] Vrable A, Chang R. Malignant melanoma of the small bowel presenting with intussusception in a woman: a case report. Melano-ma Management. 2017; 4: 99–104. https://doi.org/10.2217/mmt-2016-0028.

[28] Wu F, Lee MS, Kim DE. Small bowel obstruction caused by hemorrhagic metastatic melanoma: case report and literature review. Journal of Surgical Case Reports. 2022; 2022: rjac395. https://doi.org/10.1093/jscr/rjac395.

[29] Reddy P, Walker C, Afonso B. A rare case of metastatic malignant melanoma to the colon from an unknown primary. Case Re-ports in Gastrointestinal Medicine. 2014; 2014: 312902. https://doi.org/10.1155/2014/312902.

[30] Yuan Z, Guo HY, Lu WT, Wang YH, He J, Zhang F, *et al*. Report on a case of liver-originating malignant melanoma of unknown primary. Open Life Sciences. 2023; 18: 20220750. https://doi.org/10.1515/biol-2022-0750.

[31] Wang W, Liu J, Kang Y. Diffuse hepatic infiltration of malignant melanoma of unknown primary origin. Asian Journal of Sur-gery. 2023; 46: 2168–2169. https://doi.org/10.1016/j.asjsur.2022.11.077.

[32] Cheng AC, Lin YJ, Chiu SH, Shih YL. Combined immune checkpoint inhibitors of CTLA4 and PD-1 for hepatic melanoma of unknown primary origin: A case report. World Journal of Clinical Cases. 2021; 9: 2641–2648. https://doi.org/10.12998/wjcc.v9.i11.2641.

[33] Tiong J, Rajagopalan A, Jaya J, Sritharan M. Spontaneous rupture of a solitary oligometastatic hepatic melanoma. BMJ Case Re-ports. 2023; 16: e252367. https://doi.org/10.1136/bcr-2022-252367.

[34] Onozawa H, Saito M, Yoshida S, Sakuma T, Matsuzaki M, Katagata N, *et al*. Multiple metastatic malignant melanoma presenting intraluminal gallbladder bleeding. International Surgery. 2014; 99: 600–605. https://doi.org/10.9738/INTSURG-D-13-00143.1.

[35] Ben Slama S, Bacha D, Bayar R, Gharbi L, Lahmar A. Pancreatic resection for isolated metastasis from melanoma of unknown primary. Acta Gastro-enterologica Belgica. 2017; 80: 323–324.

[36] Nguyen V, Aboulenain S, Mohammed S, Perez Parra S. A Case of Metastatic CNS Melanoma of Unknown Primary Presenting with Seizures. Case Reports in Medicine. 2022; 2022: 3099750. https://doi.org/10.1155/2022/3099750.

[37] Garcia-Ramiu K, Mohsin I, Ikeguchi A, Newberry B. An Unusual Case of Malignant Melanoma with Metastasis to the Placenta During Pregnancy. European Journal of Case Reports in Internal Medicine. 2022; 9: 003490. https://doi.org/10.12890/2022_003490.

[38] Sawalha A, Alkilani H. Leptomeningeal Disease and Hydrocephalus as the First Presentation of Melanoma. Cureus. 2023; 15: e44648. https://doi.org/10.7759/cureus.44648.

[39] Naing A, Messina JL, Vrionis FR, Daud AI. Uncommon manifestations of common malignancies: case 3. Malignant melanoma arising from a spinal nerve root. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2004; 22: 3194–3195. https://doi.org/10.1200/JCO.2004.09.021.

[40] Chen L, Newby C, Fakhri N, Lammle M. Metastatic melanoma of unknown origin mimicking neurofibromatosis. Radiology Case Reports. 2021; 16: 119–122. https://doi.org/10.1016/j.radcr.2020.08.034.

[41] Pujani M, Hassan MJ, Jetley S, Raina PK, Kumar M. Malignant Melanoma Presenting as a Mediastinal Malignant Melanoma Presenting as a Mediastinal Unknown Primary Origin? Turk Patoloji Dergisi. 2017; 33: 168–170. https://doi.org/10.5146/tjpath.2014.01290.

[42] Kuriakose R, Melvani R, Gangadharan V, Cowley M. Right atrial metastatic melanoma with unknown primaries. Case Reports in Cardiology. 2015; 2015: 483520. https://doi.org/10.1155/2015/483520.

[43] El Haj NI, Hafidi S, Karam R, Boubia S, Karkouri M, Ridai M. Thoracic metastasis of malignant melanoma of unknown primary: A case report and literature review. International Journal of Surgery Case Reports. 2021; 87: 106383. https://doi.org/10.1016/j.ijscr.2021.106383.

[44] Tsaknis G, Naeem M, Singh A, Vijayakumar S. Malignant melanoma

without primary, presenting as solitary pulmonary nodule: a case report. Journal of Medical Case Reports. 2021; 15: 347. https://doi.org/10.1186/s13256-021-02933-z.

[45] Gebauer K, Schirren J, Jaeschke B, Kaufmann R, Meissner M. Neoadjuvant therapy with vemurafenib in Horner's syndrome as a very rare first diagnosis of a malignant melanoma of unknown primary. Journal Der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology: JDDG. 2020; 18: 47–49. https://doi.org/10.1111/ddg.13983.

[46] Azoury SC, Crompton JG, Straughan DM, Klemen ND, Reardon ES, Beresnev TH, *et al*. Unknown primary nasopha-ryngeal melanoma presenting as severe recurrent epistaxis and hearing loss following treatment and remission of metastatic disease: A case report and literature review. International Journal of Surgery Case Reports. 2015; 10: 232–235. https://doi.org/10.1016/j.ijscr.2015.03.053.

[47] Kim BC, Kang HK, Kim YS, Haw S, Kim HS, Kang J. A rare case of endobronchial melanoma of unknown primary. Respirato-ry Medicine Case Reports. 2023; 42: 101811. https://doi.org/10.1016/j.rmcr.2023.101811.

[48] Diamantopoulos P, Patavoukas G, Garantzioti A, Charakopoulos E, Kyriakakis G, Mikou P, *et al*. Melanuria in a patient with BRAF-mutant metastatic melanoma of unknown primary: Insights on the pathophysiology, differential diagnosis, prognosis, and treatment. The American Journal of the Medical Sciences. 2023; 365: 401–405. https://doi.org/10.1016/j.amjms.2022.12.012.

[49] Meng MV, Werboff LH. Hematospermia as the presenting symptom of metastatic malignant melanoma of unknown primary origin. Urology. 2000; 56: 330. https://doi.org/10.1016/s0090-4295(00)00634-8.

[50] Fabiani A, Principi E, Filosa A, Fioretti F, Maurelli V, Servi L, *et al*. Ultrasound features of a metastatic seminal vesicle melanoma: A case report. Archivio Italiano Di Urologia, Andrologia: Organo Ufficiale [di] Societa Italiana Di Ecografia Urologica E Nefrologica. 2016; 88: 347–349. https://doi.org/10.4081/aiua.2016.4.347.

[51] Tang Y, Su YC. Multiple bone metastases from an amelanotic melanoma of unknown primary origin. The Kaohsiung Journal of Medical Sciences. 2019; 35: 125–126. https://doi.org/10.1002/kjm2.12019.

[52] Kakutani K, Doita M, Nishida K, Miyamoto H, Kurosaka M. Radiculopathy due to malignant melanoma in the sacrum with unknown primary site. European Spine Journal: Official Publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. 2008; 17 Suppl 2: S271–S274. https://doi.org/10.1007/s00586-007-0561-1.

[53] Matsumoto K, Kikuchi K, Kikuyama T, Saito G, Adachi T, Watanabe A, *et al*. Disseminated Bone Marrow Carcinomato-sis Due to Malignant Melanoma of Unknown Primary Origin. Internal Medicine (Tokyo, Japan). 2021; 60: 3469–3472. https://doi.org/10.2169/internalmedicine.7274-21.

[54] Suzuki T, Kusumoto S, Iida S, Tada T, Mori F. Amelanotic malignant melanoma of unknown primary origin metastasizing to the bone marrow: a case report and review of the literature. Internal Medicine (Tokyo, Japan). 2014; 53: 325–328. https://doi.org/10.2169/internalmedicine.53.1412.

[55] Andrianandrasana NOTF, Randrianarisoa RMF, Navoly P, Ranaivoson MAC, Vololontiana HMD, Rafaramino F. Melanoma of unknown primary origin with skeletal muscle metastasis: a case report. Journal of Medical Case Reports. 2023; 17: 90. https://doi.org/10.1186/s13256-023-03813-4.

[56] Grech A, Mercieca N, Calleja-Agius J, Abela R. Metastatic malignant melanoma of unknown primary in temporalis muscle. Jour-nal of Surgical Case Reports. 2020; 2020: rjaa202. https://doi.org/10.1093/jscr/rjaa202.

[57] Dalle Carbonare M, Goh MX, AlshiekhAli Z, Howlett D. Metastatic melanoma of unknown primary in the temporalis muscle. BMJ Case Reports. 2017; 2017: bcr2017221577. https://doi.org/10.1136/bcr-2017-221577.

[58] Rastrelli M, Pigozzo J, di Maggio A, Tosi AL, Sileni VC, Rossi CR. Neoadjuvant treatment with dabrafenib of unresectable localizations from occult melanoma. Melanoma Research. 2014; 24: 413–414. https://doi.org/10.1097/CMR.0000000000000083.

[59] Gorris S, Perdaens C, Delvaux V, Poorten VV, Neyns B, Baron I. A Solitary Melanoma Metastasis Confined to the Submandib-ular Gland. Case Reports in Oncology. 2021; 14: 957–962. https://doi.org/10.1159/000516796.

[60] Drouet C, Morel O, Boulahdour H. Bilateral Huge Incidentalomas of Isolated Adrenal Metastases From Unknown Primary Mel-anoma Revealed by 18F-FDG PET/CT. Clinical Nuclear Medicine. 2017; 42: e51–e53. https://doi.org/10.1097/RLU.0000000000001417.

[61] Blanco R, Rodríguez Villar D, Fernández-Pello S, Baldissera JV, Diaz B, Venta V, *et al*. Massive bilateral adrenal meta-static melanoma of occult origin: a case report. Analytical and Quantitative Cytopathology and Histopathology. 2014; 36: 51–54.

[62] Rieth JM, Bowen RC, Milhem MM, Boldt HC, Binkley EM. Presumed Melanoma of Unknown Primary Origin Metastatic to the Choroid Mimics Primary Uveal Melanoma. Case Reports in Ophthalmology. 2021; 12: 987–993. https://doi.org/10.1159/000521199.

[63] Mondragón JD, Jiménez-Zarazúa O, Vélez-Ramírez LN, Martínez-Rivera MA, Enríquez-Maciel S, González-Guzmán J, *et al*. Paraneoplastic opsoclonus-myoclonus syndrome secondary to melanoma metastasis form occult primary cancer. Case Reports in Neu-rology. 2019; 11: 66–79. https://doi.org/10.1159/000497034.

[64] Spoto S, Crescenzi A, Taffon C, Ciccozzi M, Costantino S, Angeletti S. Where Did It Start? Subcutaneous Metastatic Melanoma. The American Journal of Medicine. 2018; 131: 41–44. https://doi.org/10.1016/j.amjmed.2017.09.011.

[65] Liu ET, Hsu CH, Chang DH. Management of advanced stage IV melanoma of unknown primary origin with multiple visceral metastases. Asian Journal of Surgery. 2024; 47: 1053–1054. https://doi.org/10.1016/j.asjsur.2023.10.103.

[66] Myrou A, Aslanidis T, Protopapas A, Psoma E, Kontosis A, Koletsa T. Primary gastric melanoma of unknown origin: a case re-port and short literature review. Folia Medica. 2021; 63: 282–286. https://doi.org/10.3897/folmed.63.e53726.

[67] Jin Y, Ran C, Li F, Cheng N. Melanoma of unknown primary in the pancreas: should it be considered primary? BMC Surgery. 2020; 20: 76. https://doi.org/10.1186/s12893-020-00731-w.

[68] Rice-Canetto TE, Richard D, Kim G, Ramnot A, Siddiqi J. Melanoma of Unknown Primary With Metastasis to the Brain: A Case Report and Review of the Literature. Cureus. 2024; 16: e67022. https://doi.org/10.7759/cureus.67022.

[69] Proboka G, Tilgase A, Isajevs S, Rasa A, Alberts P. Melanoma Unknown Primary Brain Metastasis Treatment with ECHO-7 Oncolytic Virus Rigvir: A Case Report. Frontiers in Oncology. 2018; 8: 43. https://doi.org/10.3389/fonc.2018.00043.

[70] Shan GD, Xu GQ, Chen LH, Wang ZM, Jin EY, Hu FL, *et al*. Diffuse liver infiltration by melanoma of unknown prima-ry origin: one case report and literature review. Internal Medicine (Tokyo, Japan). 2009; 48: 2093–2096. https://doi.org/10.2169/internalmedicine.48.2542.

[71] Ejaz S, Shawa H, Henderson SA, Habra MA. Melanoma of unknown primary origin presenting as a rapidly enlarging adrenal mass. BMJ Case Reports. 2013; 2013: bcr2013009727. https://doi.org/10.1136/bcr-2013-009727.

[72] González-de Arriba M, Bordel-Gómez MT, Solera JC, Sánchez-Estella J. Primary dermal melanoma: a case report and a review of the literature. Actas Dermo-sifiliograficas. 2013; 104: 518–522. https://doi.org/10.1016/j.ad.2011.12.020. (In English, Spanish)

[73] Shenoy AS, Desai HM, Kavishwar VS, Savant HV. Metastatic malignant melanoma in a young adult with unknown primary. Indian Journal of Cancer. 2015; 52: 446–447. https://doi.org/10.4103/

0019-509X.176748.
[74] Dhandha M, Chu MB, Richart JM. Coexistent metastatic melanoma of the kidney with unknown primary and renal cell carcino-ma. BMJ Case Reports. 2012; 2012: bcr2012007286. https://doi.org/10.1136/bcr-2012-007286.
[75] Gaballa S, Hlaing KM, Mahler N, Moursy S, Ahmed A. A Rare Case of Immune-Mediated Primary Adrenal Insufficiency With Cytotoxic T-Lymphocyte Antigen-4 Inhibitor Ipilimumab in Metastatic Melanoma of Lung and Neck of Unknown Primary. Cureus. 2020; 12: e8602. https://doi.org/10.7759/cureus.8602.
[76] Christopoulos P, Doulias T, Koutelidakis I, Papaziogas B. Stage IV malignant melanoma of unknown primary site in a young man. BMJ Case Reports. 2012; 2012: bcr2012006283. https://doi.org/10.1136/bcr-2012-006283.
[77] Matull J, Livingstone E, Wetter A, Zimmer L, Zaremba A, Lahner H, *et al*. Durable Complete Response in a Melanoma Patient With Unknown Primary, Associated With Sequential and Severe Multi-Organ Toxicity After a Single Dose of CTLA-4 Plus PD-1 Blockade: A Case Report. Frontiers in Oncology. 2020; 10: 592609. https://doi.org/10.3389/fonc.2020.592609.
[78] Malafronte P, Sorrells T. Lymph node melanosis in a patient with metastatic melanoma of unknown primary. Archives of Pathol-ogy & Laboratory Medicine. 2009; 133: 1332–1334. https://doi.org/10.5858/133.8.1332.
[79] Lewis KD, Dollarhide S, Fitzpatrick JE, Gonzalez R, High WA, McCarter MD, *et al*. Metastatic malignant melanoma from an unknown primary presenting as a large axillary mass. Oncology (Williston Park, N.Y.). 2006; 20: 763–770.
[80] Tanaka K, Tomita H, Hisamatsu K, Hatano Y, Yoshida K, Hara A. Acute Liver Failure Associated with Diffuse Hepatic Infiltration of Malignant Melanoma of Unknown Primary Origin. Internal Medicine (Tokyo, Japan). 2015; 54: 1361–1364. https://doi.org/10.2169/internalmedicine.54.3428.
[81] Hedayati AA, Bandurski J, Lewandowski A. Bifocal metastasis of melanoma to the small intestine from an unknown primary with intestinal obstruction - case report. Contemporary Oncology (Poznan, Poland). 2013; 17: 317–320. https://doi.org/10.5114/wo.2013.35285.
[82] Pabianek M, Jatczak-Grochala I, Lesiak A, Narbutt J, Siekierko A, Stasikowska-Kanicka O, *et al*. Isolated melanoma me-tastasis in a patient with large congenital nevus without detectable primary melanoma: a case report and review of literature. Frontiers in Medicine. 2024; 11: 1427982. https://doi.org/10.3389/fmed.2024.1427982.
[83] Moorchung N, Mukherjee B, Srinivas V, Subramanya H. Metastatic Amelanotic Malignant Melanoma with Unknown Primary - A Case Report. Medical Journal, Armed Forces India. 2004; 60: 295–296. https://doi.org/10.1016/S0377-1237(04)80070-4.
[84] Sethi A, Raj M. Pembrolizumab-Induced Lichenoid Dermatitis in a Patient With Metastatic Cancer of Unknown Primary. Cureus. 2021; 13: e13768. https://doi.org/10.7759/cureus.13768.
[85] Chantharasamee J, Treetipsatit J. Metastatic Melanoma of Uncertain Primary with 5-Year Durable Response after Conventional Therapy: A Case Report with Literature Review. Case Reports in Oncological Medicine. 2018; 2018: 7289896. https://doi.org/10.1155/2018/7289896.
[86] Singh R, Torre K, Farooq H, Chang V. Large Necrotic Mass in the Small Bowel. ACG Case Reports Journal. 2020; 7: e00393. https://doi.org/10.14309/crj.0000000000000393.
[87] Bordeanu-Diaconescu EM, Cretu A, Grosu-Bularda A, Andrei MC, Hodea FV, Dumitru CS, *et al*. Comprehensive Liter-ature Review on Melanoma of Unknown Primary Site Triggered by an Intriguing Case Report. Diagnostics (Basel, Switzerland). 2024; 14: 2210. https://doi.org/10.3390/diagnostics14192210.
[88] Vilar A, Serrano E, Brabyn P, Diez MM, Gutierrez A. Multiple giant cutaneous metastasis and ileal intussusception from an un-known melanoma: A case report. Medicine International. 2024; 4: 51. https://doi.org/10.3892/mi.2024.175.
[89] Verhulst D, Demaerel P, Damato B, Leys A. Bilateral ocular metastasis from an occult primary melanoma. The British Journal of Ophthalmology. 2006; 90: 922–923. https://doi.org/10.1136/bjo.2006.092445.
[90] Onan B, Onan IS, Polat B. Surgical resection of solitary metastasis of malignant melanoma to the right atrium. Texas Heart Insti-tute Journal. 2010; 37: 598–601.
[91] Chew SM, Lucas M, Brady M, Kelly CM. SKAP2-BRAF fusion and response to an MEK inhibitor in a patient with metastatic melanoma resistant to immunotherapy. BMJ Case Reports. 2021; 14: e238494. https://doi.org/10.1136/bcr-2020-238494.
[92] Patel RB, Vasava NC, Gandhi MB. Acute small bowel obstruction due to intussusception of malignant amelonatic melanoma of the small intestine. BMJ Case Reports. 2012; 2012: bcr2012006352. https://doi.org/10.1136/bcr-2012-006352.
[93] Navarrete-Dechent C, Monnier J, Marghoob NG, Liopyris K, Busam KJ, Francis JH, *et al*. Bilateral diffuse uveal mela-nocytic proliferation with multifocal diffuse integumentary melanocytic proliferation paraneoplastic syndrome: A case report. The Australa-sian Journal of Dermatology. 2021; 62: 386–389. https://doi.org/10.1111/ajd.13617.
[94] Papoutsoglou N, Burger M, Riedmiller H. Persistent painless hemospermia due to metastatic melanoma of the right seminal vesi-cle. BMC Urology. 2013; 13: 43. https://doi.org/10.1186/1471-2490-13-43.
[95] Rapisuwon S, Busam KJ, Parks K, Chapman PB, Lee E, Atkins MB. Discordance Between Cobas BRAF V600 Testing and VE1 Immunohistochemistry in a Melanoma Patient With Bone Marrow Metastases. The American Journal of Dermatopathology. 2016; 38: 687–689. https://doi.org/10.1097/DAD.0000000000000660.
[96] Deng X, Xiang K, He X, Chen S, Guo Q, Wu H, *et al*. Good response of stage IV melanoma to high dose radiation ther-apy combined with immunotherapy: A case report. Oncology Letters. 2024; 28: 598. https://doi.org/10.3892/ol.2024.14731.
[97] Ontiveros Ramírez D, Ramírez Alvarado CA, Ramírez Gonzalez MA, Carballar Mejía F, Maldonado Mares S. An Intestinal Melanoma of Unknown Origin Presenting as an Intussusception: A Case Report of a Rare Entity. Cureus. 2025; 17: e80032. https://doi.org/10.7759/cureus.80032.
[98] ShamaeiZadeh P, Campbell E, Comfere N. The Utility of Radiologic Imaging and Full Body Skin Examination in Patients With Melanoma of Unknown Primary. Cureus. 2024; 16: e58523. https://doi.org/10.7759/cureus.58523.
[99] Jiménez-Zarazúa O, Vélez-Ramírez LN, Alcocer-León M, Hernández-Domínguez DA, Tadeo-González JE, Martínez-Rivera MA, *et al*. Paraneoplastic Cerebellar Degeneration Secondary to BRAF Mutant Melanoma Metastasis from an Occult Primary Cancer. Case Reports in Oncology. 2020; 13: 633–642. https://doi.org/10.1159/000507729.
[100] Krishna Mohan MVT, Rajappa SJ, Reddy TV, Paul TR. Malignant gastrointestinal melanoma with an unknown primary. Indian Journal of Medical and Paediatric Oncology: Official Journal of Indian Society of Medical & Paediatric Oncology. 2009; 30: 87–89. https://doi.org/10.4103/0971-5851.60055.
[101] Cho EA, Lee MA, Kang H, Lee SD, Kim HO, Park YM. Vitiligo-like Depigmentation Associated with Metastatic Melanoma of an Unknown Origin. Annals of Dermatology. 2009; 21: 178–181. https://doi.org/10.5021/ad.2009.21.2.178.
[102] Dalal MD, Morgans CW, Duvoisin RM, Gamboa EA, Jeffrey BG, Garg SJ, *et al*. Diagnosis of occult melanoma using transient receptor potential melastatin 1 (TRPM1) autoantibody testing: a novel approach. Ophthalmology. 2013; 120: 2560–2564. https://doi.org/10.1016/j.ophtha.2013.07.037.
[103] Osella-Abate S, Conti L, Annaratone L, Senetta R, Bertero L, Lic-

ciardello M, *et al*. Phenotypic characterisation of im-mune cells associated with histological regression in cutaneous melanoma. Pathology. 2019; 51: 487–493. https://doi.org/10.1016/j.pathol.2019.04.001.

[104] Aung PP, Nagarajan P, Prieto VG. Regression in primary cutaneous melanoma: etiopathogenesis and clinical significance. La-boratory Investigation; a Journal of Technical Methods and Pathology. 2017; 97: 657–668. https://doi.org/10.1038/labinvest.2017.8.

[105] Blanc F, Bertho N, Piton G, Leplat JJ, Egidy G, Bourneuf E, *et al*. Deciphering the immune reaction leading to sponta-neous melanoma regression: initial role of MHCII^{+} CD163^{-} macrophages. Cancer Immunology, Immunotherapy: CII. 2023; 72: 3507–3521. https://doi.org/10.1007/s00262-023-03503-6.

[106] Reschke R, Enk AH, Hassel JC. Chemokines and Cytokines in Immunotherapy of Melanoma and Other Tumors: From Bi-omarkers to Therapeutic Targets. International Journal of Molecular Sciences. 2024; 25: 6532. https://doi.org/10.3390/ijms25126532.

[107] Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, *et al*. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA: A Cancer Journal for Clinicians. 2017; 67: 472–492. https://doi.org/10.3322/caac.21409.

[108] Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, *et al*. Final version of 2009 AJCC mela-noma staging and classification. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2009; 27: 6199–6206. https://doi.org/10.1200/JCO.2009.23.4799.

[109] Keung EZ, Gershenwald JE. The eighth edition American Joint Committee on Cancer (AJCC) melanoma staging system: implications for melanoma treatment and care. Expert Review of Anticancer Therapy. 2018; 18: 775–784. https://doi.org/10.1080/14737140.2018.1489246.

[110] Bae JM, Choi YY, Kim DS, Lee JH, Jang HS, Lee JH, *et al*. Metastatic melanomas of unknown primary show better prognosis than those of known primary: a systematic review and meta-analysis of observational studies. Journal of the American Academy of Dermatology. 2015; 72: 59–70. https://doi.org/10.1016/j.jaad.2014.09.029.

[111] van der Ploeg APT, Haydu LE, Spillane AJ, Scolyer RA, Quinn MJ, Saw RPM, *et al*. Melanoma patients with an un-known primary tumor site have a better outcome than those with a known primary following therapeutic lymph node dissection for macro-scopic (clinically palpable) nodal disease. Annals of Surgical Oncology. 2014; 21: 3108–3116. https://doi.org/10.1245/s10434-014-3679-5.

[112] Tarhini AA, Lee SJ, Tan AC, El Naqa IM, Stephen Hodi F, Butterfield LH, *et al*. Improved prognosis and evidence of enhanced immunogenicity in tumor and circulation of high-risk melanoma patients with unknown primary. Journal for Immunotherapy of Cancer. 2022; 10: e004310. https://doi.org/10.1136/jitc-2021-004310.

[113] Scott JF, Conic RZ, Thompson CL, Gerstenblith MR, Bordeaux JS. Stage IV melanoma of unknown primary: A population-based study in the United States from 1973 to 2014. Journal of the American Academy of Dermatology. 2018; 79: 258–265.e4. https://doi.org/10.1016/j.jaad.2018.03.021.

[114] Cormier JN, Xing Y, Feng L, Huang X, Davidson L, Gershenwald JE, *et al*. Metastatic melanoma to lymph nodes in patients with unknown primary sites. Cancer. 2006; 106: 2012–2020. https://doi.org/10.1002/cncr.21835.

[115] Shi A, Yan M, Pang B, Pang L, Wang Y, Lan Y, *et al*. Dissecting cellular states of infiltrating microenvironment cells in melanoma by integrating single-cell and bulk transcriptome analysis. BMC Immunology. 2023; 24: 52. https://doi.org/10.1186/s12865-023-00587-8.

[116] Georgoulias G, Zaravinos A. Genomic landscape of the immunogenicity regulation in skin melanomas with diverse tumor mutation burden. Frontiers in Immunology. 2022; 13: 1006665. https://doi.org/10.3389/fimmu.2022.1006665.

[117] Pilla L, Alberti A, Di Mauro P, Gemelli M, Cogliati V, Cazzaniga ME, *et al*. Molecular and Immune Biomarkers for Cu-taneous Melanoma: Current Status and Future Prospects. Cancers. 2020; 12: 3456. https://doi.org/10.3390/cancers12113456.

[118] Seth R, Agarwala SS, Messersmith H, Alluri KC, Ascierto PA, Atkins MB, *et al*. Systemic Therapy for Melanoma: ASCO Guideline Update. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2023; 41: 4794–4820. https://doi.org/10.1200/JCO.23.01136.

[119] Lopez R, Holyoke ED, Moore RH, Karakousis CP. Malignant melanoma with unknown primary site. Journal of Surgical On-cology. 1982; 19: 151–154. https://doi.org/10.1002/jso.2930190308.

[120] Reintgen DS, McCarty KS, Woodard B, Cox E, Seigler HF. Metastatic malignant melanoma with an unknown primary. Sur-gery, Gynecology & Obstetrics. 1983; 156: 335–340.

[121] Klausner JM, Gutman M, Inbar M, Rozin RR. Unknown primary melanoma. Journal of Surgical Oncology. 1983; 24: 129–131. https://doi.org/10.1002/jso.2930240213.

[122] Rousset P, Dalle S, Mortier L, Dereure O, Dalac S, Dutriaux C, *et al*. Impact of systemic therapies in metastatic melano-ma of unknown primary: A study from MELBASE, a French multicentric prospective cohort. Journal of the American Academy of Der-matology. 2023; 88: 808–815. https://doi.org/10.1016/j.jaad.2022.11.040.

[123] Boussios S, Rassy E, Samartzis E, Moschetta M, Sheriff M, Pérez-Fidalgo JA, *et al*. Melanoma of unknown primary: New perspectives for an old story. Critical Reviews in Oncology/hematology. 2021; 158: 103208. https://doi.org/10.1016/j.critrevonc.2020.103208.

[124] Gambichler T, Chatzipantazi M, Schröter U, Stockfleth E, Gedik C. Patients with melanoma of unknown primary show better outcome under immune checkpoint inhibitor therapy than patients with known primary: preliminary results. Oncoimmunology. 2019; 8: e1677139. https://doi.org/10.1080/2162402X.2019.1677139.

[125] Verver D, van der Veldt A, van Akkooi A, Verhoef C, Grünhagen DJ, Louwman WJ. Treatment of melanoma of unknown pri-mary in the era of immunotherapy and targeted therapy: A Dutch population-based study. International Journal of Cancer. 2020; 146: 26–34. https://doi.org/10.1002/ijc.32229.