UDC 616.5-006.81-033.2-06:616-003.829-031.81]-07-089
DOI http://doi.org/10.30978/GS-2025-2-56

ISSN 2786-5584 PRINT
ISSN 2786-5592 ONLINE

Clinical approach to the treatment of metastatic skin melanoma. Case study

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Melanoma is an aggressive disease that accounts for approximately 75 % of skin cancer-related deaths. The primary objectives of surgery in metastatic disease are symptom relief and debulking. As effective systemic treatment prolongs survival in a patient population with advanced disease, the role of local palliative therapy potentially increases. When considering palliative surgery, it is crucial to weigh the potential risks of surgical complications against the burden caused by the symptomatic lesions.

We present a case report of melanoma TxNxM1c metastasis to the skin in the right supraclavicular area with disintegration and bleeding, metastatic lesions in the cervical, axillary, and subpectoral lymph nodes bilaterally, and metastatic lesions in the left adrenal gland, stage IV. The patient was urgently hospitalized with manifestations of diffuse bleeding associated with tumor disintegration. According to the treatment history, the patient has been receiving targeted chemo-immunotherapy since 2022. The pain syndrome intensified, and periodic episodes of bleeding from the tumor were observed. Cytoreductive surgery tactics were discussed by the multidisciplinary team and agreed upon with the patient. The patient insisted on removing the tumor despite the risks of the operation. This clinical study deals with a controversial, yet clinically required, palliative care method for preserving and improving the quality of life with this diagnosis. This case highlights the aggressive nature of generalized melanosis, characterized by a rapid clinical course and limited response to traditional targeted chemo-immunotherapy. The difficulties encountered in the diagnosis and treatment of this aggressive form of metastatic melanoma underscore the need for early detection, tailored therapeutic approaches, and ongoing research efforts to improve treatment outcomes in such cases.

Keywords
melanoma, metastasectomy, systemic therapy, surgery treatment.

ARTICLE • Received 2025-03-25 • Received in revised form 2025-04-22 • Published 2025-07-31

Melanoma is a malignant neoplasm that develops from pigment cells (melanocytes) and most often affects the skin [6].

The annual incidence of malignant skin melanoma (MS) ranges from 3–5 per 100,000 population (Mediterranean countries) to 12–35 per 100,000 (Nordic countries), while in Australia and New Zealand it can reach 50 per 100,000 population. It is noted that the incidence of melanoma has been steadily increasing over the past 40 years, with a tendency to stabilize the mortality rate, except in elderly men. The peak incidence of cutaneous melanoma occurs at age 65, although the disease can occur at any age. There is also an increase in the mortality-to-incidence ratio in Eastern European countries compared to Western European countries, which indicates the need to improve prevention measures and early detection of melanoma in Eastern European countries, in particular in Ukraine. In 2022, 330,000 new cases of melanoma were diagnosed worldwide, and almost 60,000 people died from this disease [1]. According to the National Cancer Registry, 5,051 cases of melanoma were registered in Ukraine in 2022–2023. As of 2023, 31,217 people with this disease were registered. Of those newly diagnosed, 33.9 % had stage

I of the disease, 43.4 % had stage II, 6.9 % had stage III, and 5.3 % had stage IV; in 10.4 % of patients, the stage was not determined. Treatment of metastatic melanoma is challenging. Overall 1-year survival for metastatic (generalized) melanoma depends on the stage of spread and is 62 % for stage M1a, 53 % for M1b, and 33 % for M1c [2]. Surgery for stage IV melanoma remains controversial, with systemic therapy being preferred. However, the need for rapid removal of life-threatening metastases and improved patient quality of life supports the need for surgical removal of the tumor, but it does not confer any survival advantage [3, 5].

Case report

Female patient, born in 1966.

Diagnosis: Non-pigmented melanoma TxNxM1c metastasis to the skin in the right supraclavicular area with disintegration and bleeding, metastatic lesions in the cervical, axillary, and subpectoral lymph nodes bilaterally, and metastatic lesions in the left adrenal gland, stage IV.

From the anamnesis: the diagnosis of non-pigmented melanoma was established in 2017, when a neoplasm in the right subscapular area was removed. The patient did not receive specific treatment in the postoperative period.

In 2022, the diagnosis was made: metastatic melanoma of the skin of the left breast, BRAF V600 mutated. 17 courses of radiation therapy (42.6 Gy) were performed, followed by 6 months of targeted therapy with encorafenib + binimetinib.

From March to May 2023, 4 courses of nivolumab immunotherapy were conducted.

In April 2024, the patient reported an enlargement of the supraclavicular and right cervical lymph nodes.

In July 2024, the patient began receiving pembrolizumab immunotherapy.

In October 2024, the patient was urgently hospitalized with manifestations of diffuse bleeding associated with tumor disintegration. The bleeding was stopped (Fig. 1).

The patient's general condition stabilized as a result of the treatment. Bandages with antiseptics were applied to the tumor, antibiotic therapy was administered based on bacterial culture results, and targeted therapy was prescribed according to the oncologist's recommendations (encorafenib + binimetinib).

Periodically, the patient had recurrent bleeding, which was stopped by tight tamponade and the use of hemostatic sponges. The pain syndrome intensified. Preoperative preparation was performed.

According to computed tomography (Fig. 2): Tumor mass in the right supraclavicular area with disintegration 160 × 161 mm, signs of vascular invasion of small branches of the right subclavian artery, invasion of the common, external, and internal carotid arteries, jugular vein, adjacent muscles, and the right lobe of the thyroid gland.

Metastatic lesions in the cervical, axillary, and subpectoral lymph nodes bilaterally; metastatic lesions in the left adrenal gland with tumor invasion of the left renal artery and vein; contact with the celiac trunk and left gastric artery.

Brain: No additional formations or foci of pathological density were detected. No additional formations or infiltrative changes in the lungs were detected. Mediastinal organs without visible pathology. Intrathoracic and axillary lymph nodes were not enlarged.

In November 2024, surgical treatment was performed in the following scope: Cytoreductive removal of skin melanoma in the right supraclavicular area. Plastic surgery with a skin-muscular flap on the vascular pedicle. The course of the postoperative period was of moderate severity. The postoperative wound healed with primary tension.

January 2025. Disease progression: a local metastatic lesion in the postoperative scar with compression of the tissues and organs in the neck. Tracheostomy. Symptomatic treatment. January 2025: death of the patient.

Figure 1. **Preoperative appearance of the tumor**

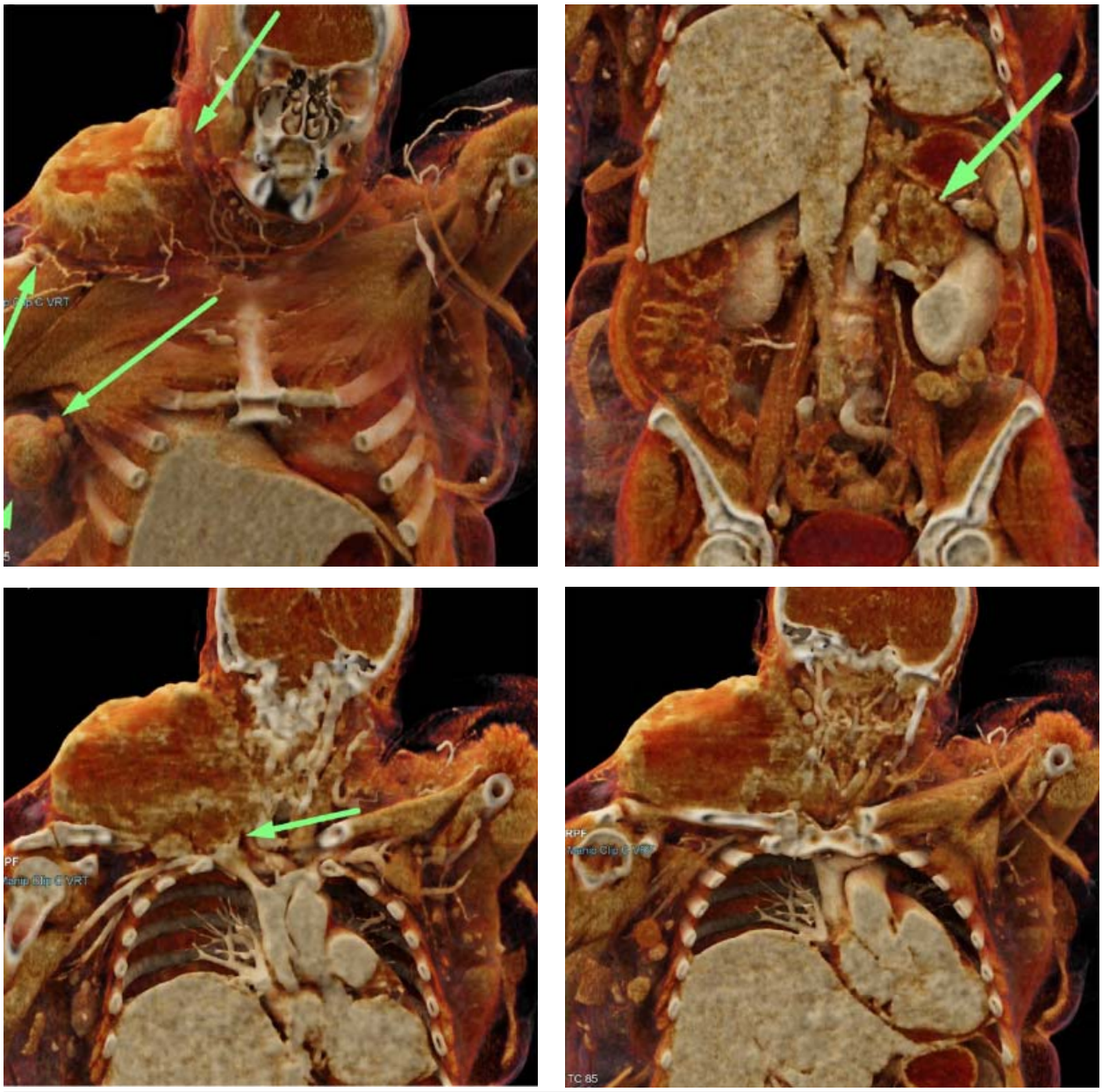

Figure 2. **Preoperative computed tomography results**

Discussion

This clinical case demonstrates a multifaceted approach to palliative treatment of skin melanoma, wherein systemic treatment serves as the primary therapeutic modality necessitating surgical intervention to eliminate the risk of blood loss and improve the patient's quality of life amidst the decay of necrotic tumor masses.

The role of metastasectomy in the treatment of melanoma varies depending on the site of metastasis and the patient's unique clinical presentation and may serve as an adjunct to systemic treatment of patients.

Approximately 50 % of melanomas exhibit BRAFV600 mutations. The occurrence of BRAF mutations varies depending on tumor location, with the highest frequency observed on the trunk (57 %), extremities (46 %), and face or scalp (28 %).

Targeted therapies for melanoma with the BRAF V600E mutation have shown significant clinical results, although these are often temporary.

In addition, ongoing studies are investigating the combination of immune checkpoint inhibitors and targeted therapy, used simultaneously or sequentially [6].

Nivolumab is a human IgG4 monoclonal antibody that blocks the PD-1 protein. It is a type of immunotherapy that works as a checkpoint inhibitor, blocking the signal that prevents T cells from activating

Figure 3. **Macroscopic specimen of the tumor and postoperative appearance of the wound**

against tumor cells. Nivolumab is used as a second-line drug for unresectable or metastatic melanoma after treatment with ipilimumab and, if the cancer has a BRAF mutation, a BRAF inhibitor [4].

Pembrolizumab is a humanized monoclonal antibody preparation against PD-1 (cell death protein 1), an immune checkpoint inhibitor that blocks the binding of PD-1 to the PD-L1 and PD-L2 ligands and thus restores the immune system's ability to attack and destroy cancer cells. Based on the results of the KEYNOTE-006 study, pembrolizumab was approved for use in unresectable and metastatic melanoma. Regarding the BRAF mutation, the results of the KEYNOTE 054 study showed that the efficacy of pembrolizumab was independent of the presence or absence of this mutation [8].

Encorafenib (BRAFTOVI) and binimetinib (MEKTOVI) were approved by the FDA in 2018 as a combination therapy based on results from the phase 3 COLUMBUS trial, which showed improved progression-free survival (14.9 months) in 577 previously untreated patients or those who have experienced disease progression at the start of or after prior first-line immunotherapy, compared with vemurafenib monotherapy (the mechanism of action of which is selective inhibition of mutant BRAF protein, with a particular focus on the V600E mutation, which is common in approximately 45 % of melanoma cases) (7.3 months) with a median follow-up of 16.6 months and improved tolerability of the combination regimen. A subsequent interim analysis of overall survival with a median follow-up of 36.8 months showed a median OS of 33.6 months with encorafenib plus binimetinib versus 16.9 months with vemurafenib (HR= 0.61 [95 % CI 0.47–0.79], p< 0.0001), demonstrating clinically meaningful efficacy and improved tolerability. Combined BRAF/MEK inhibition is the standard of care for advanced BRAF-mutated melanoma, especially with rapidly progressing and/or extensive metastases [7].

Surgery does not improve survival in patients with disseminated extracranial metastatic melanoma, but this tactic is important in most cases to preserve the patient's life and quality of life [3].

Conclusions

Palliative surgery for life-threatening metastatic skin melanoma is one of the methods of a multifaceted treatment strategy for this pathology.

Declaration of interests

The authors declare no conflicts of interest.

Ethics approval and written informed consent statements

All procedures were carried out in compliance with the current legislation of Ukraine on ethics, the principles of Good Clinical Practice (ICH GCP), and the recommendations of the 2013 Helsinki Declaration.

Authors contributions

O. I. Dronov: critical review of the manuscript;
L. O. Roshchina, Y. P. Bakunets: work concept, design, and critical review of the manuscript; L. V. Levchenko: work concept and design, data collection and analysis, and writing the manuscript; V. I. Nahrebetskyi: data collection, analysis, and writing the manuscript.

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Клінічний підхід до лікування при метастатичній меланомі шкіри. Клінічний випадок

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Меланома – це агресивне захворювання, яке є причиною близько 75% смертей, пов'язаних із раком шкіри. Основні цілі хірургічного втручання при метастатичній меланомі – полегшення симптомів та зменшення об'єму пухлини. На тлі системної терапії, що демонструє поліпшення виживаності пацієнтів із цією патологією, роль локальної паліативної терапії потенційно зростає. Розглядаючи питання щодо застосування паліативної хірургії, важливо знайти баланс між потенційними ризиками хірургічних ускладнень і ризиками, спричиненими симптоматичними ураженнями.

Представлено клінічний випадок меланоми TxNxM1c. Метастази шкіри правої надключичної ділянки з розпадом та кровотечею. Білатеральне метастатичне ураження шийних, пахвових, грудних лімфатичних вузлів, метастатичне ураження лівого надниркника, IV стадія. Пацієнтка госпіталізована в клініку в ургентному порядку з виявами дифузної кровотечі на тлі розпаду пухлини. З анамнезу лікування пацієнтки відомо, що з 2022 року розпочато прийом курсів таргетної хіміо-імунотерапії. Больовий синдром підсилювався, спостерігалися періодичні епізоди кровотечі з пухлини. Тактика лікування в обсязі циторедуктивного видалення пухлини обговорена мультидисциплінарною командою та узгоджена з пацієнткою. Пацієнтка наполягала на видаленні пухлини, незважаючи на ризики операції. Представлений кейс хірургічного лікування метастатичної меланоми є суперечливим, але водночас клінічно необхідним методом паліативного лікування для збереження та поліпшення якості життя пацієнтки. Цей випадок свідчить про агресивний характер генералізованого меланозу, що характеризується швидким клінічним перебігом та обмеженою відповіддю на основні рекомендовані схеми таргетної хіміо-імунотерапії. З огляду на труднощі діагностики та лікування цієї агресивної форми метастатичної меланоми, важливе значення мають раннє виявлення, адаптовані терапевтичні підходи й постійні дослідницькі зусилля для поліпшення результатів лікування таких пацієнтів.

Ключові слова: меланома, метастазектомія, системне лікування, хірургічне лікування.

FOR CITATION

Dronov OI, Roshchina LO, Bakunets YP, Levchenko LV, Nahrebetskyi VI. Clinical approach to the treatment of metastatic skin melanoma. Case study. General Surgery (Ukraine). 2025;(2);56-61. http://doi.org/10.30978/GS-2025-2-56.