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Metastatic Relapse of Ewing Sarcoma with Parietal Bone Involvement and Intracranial Extension Following Euro-Ewing 2012 Protocol and Left Transfemoral Amputation

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Abstract. *Introduction*. Ewing sarcoma is a highly aggressive malignant bone tumor associated with a high risk of relapse and metastatic spread, whereas skull and intracranial involvement remains rare and clinically challenging.
Aim. The aim of this case report is to describe a late metastatic relapse of Ewing sarcoma presenting as a right parietal bone metastasis with intracranial extension 2.9 years after completion of Euro-Ewing 2012 protocol treatment and left transfemoral amputation, and to discuss implications for individualized post-remission surveillance.
Materials and Methods. An 11-year-old patient initially achieved complete clinical remission after multimodal treatment for Ewing sarcoma of the left lower limb; however, due to emergency evacuation and subsequent treatment abroad after the beginning of the full-scale invasion of Ukraine, primary diagnostic documentation was limited, and regular surveillance imaging during remission was not performed according to the available history. In August 2025, the patient was admitted with persistent fever without an identifiable infectious source and subsequently developed a painless right parietal mass with headache. Brain CT and MRI revealed osteolytic destruction of the right parietal bone with a paraosseous soft-tissue component and intracranial parameningeal extension, while histopathological examination confirmed metastatic Ewing sarcoma.
Results. Systemic staging demonstrated additional metastatic lesions in the left iliac bone and segment S5 of the right lung. Second-line treatment included high-dose ifosfamide-based chemotherapy, peripheral blood stem cell mobilization and collection, surgical resection of the cranial metastasis, and high-dose chemotherapy with autologous stem cell transplantation followed by referral for consolidative radiotherapy. After two cycles of chemotherapy, partial response was achieved according to RECIST 1.1 criteria, with reduction of the cranial, iliac, and pulmonary lesions; subsequent imaging showed complete regression of the pulmonary metastasis and stabilization of the iliac bone lesion. The cranial metastasis was resected with R0 margins, although isolated tumor cell elements were identified on the dural surface.
Conclusions. This case illustrates that Ewing sarcoma may relapse after a prolonged remission period with atypical cranial and intracranial involvement and may initially present with nonspecific symptoms. Current follow-up strategies mainly focus on the primary site and chest imaging and may fail to detect rare metastatic localizations at an early stage. Brain MRI should not be interpreted as a routine requirement for all survivors; rather, it may be considered in selected patients with neurological symptoms, cranial complaints, unexplained fever without an identifiable source, or other high-risk clinical features. Further prospective studies are required to define standardized indications for neuroimaging during long-term follow-up of Ewing sarcoma survivors.

Keywords: sarcoma, ewing; neoplasm metastasis; skull neoplasms; brain neoplasms; magnetic resonance imaging; ifosfamide; hematopoietic stem cell transplantation.

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Introduction

Ewing sarcoma (ES) is an aggressive malignant tumor predominantly affecting children, adolescents, and young adults, accounting for approximately 10–15% of primary bone sarcomas [1]. It most commonly arises in the pelvis, axial skeleton, and long bones such as the femur, presenting with nonspecific symptoms including pain and swelling, which may delay diagnosis. Despite multimodal treatment approaches combining chemotherapy, surgery, and radiotherapy, approximately 25% of patients with initially localized disease experience relapse, often associated with poor prognosis and a 5-year survival rate of about 13% [2].

At the molecular level, ES is characterized by chromosomal translocations, most commonly t(11;22)(q24;q12), resulting in the EWSR1–FLI1 fusion gene in approximately 85% of cases [3]. This aberrant transcription factor plays a central role in tumor biology, contributing to proliferation, intratumoral heterogeneity, and metastatic potential. Tumor dissemination follows a multistep cascade involving invasion, intravasation, circulation, extravasation, and colonization at distant sites. ES most frequently metastasizes to the lungs, bones, and bone marrow [4], whereas intracranial and skull involvement remain rare manifestations [5][6][7].

Although most recurrences occur within the first two years after diagnosis [8], late relapses are well documented, underscoring the need for prolonged surveillance. However, there is currently no universally accepted follow-up strategy for patients in remission, particularly regarding the detection of rare metastatic sites such as the central nervous system. Existing recommendations primarily focus on imaging of the primary tumor site and chest [9], potentially overlooking atypical patterns of disease progression.

This case highlights a rare presentation of late metastatic relapse of Ewing sarcoma with involvement of the right parietal bone and intracranial extension following a prolonged remission period. It underscores the diagnostic challenges associated with atypical metastatic spread and emphasizes the need for individualized, symptom-oriented surveillance strategies, including selective use of neuroimaging in patients with neurological symptoms, cranial complaints, unexplained fever, or other high-risk features.

Aim

To present a clinical case of late metastatic relapse of Ewing sarcoma with intracranial extension occurring 2.9 years after remission was achieved; to analyze current post-remission surveillance strategies and identify gaps in follow-up algorithms, particularly the lack of clear indications for neuroimaging in symptomatic or high-risk patients; and to discuss the role of EWSR1–FLI1 as a potential molecular driver of metastatic potential and relapse risk.

Materials and Methods

This manuscript was prepared as a single-patient clinical case report. Clinical data were obtained retrospectively from the patient's available medical records, including diagnostic imaging, histopathological findings, treatment documentation, multidisciplinary tumor board conclusions, and follow-up reports. Primary diagnostic information was limited because the patient had been evacuated from Kharkiv to Lviv and then to the United Kingdom after the beginning of the full-scale invasion of Ukraine, and only concise documentation from the initial diagnostic and treatment period was available. Imaging assessment included CT and MRI of the cranial lesion, contrast-enhanced staging CT, and post-treatment control imaging. Tumor response was evaluated according to RECIST 1.1 criteria. The clinical course, diagnostic and treatment decisions, and outcome data were described narratively and compared with published literature on relapsed Ewing sarcoma, skull metastases, and intracranial involvement. No statistical analysis was performed because this report presents a single clinical observation.

Case Presentation

An 11-year-old patient initially presented in February 2022 with complaints of periodic pain in the left lower limb, primarily in the femoral and gluteal regions. The condition was initially misinterpreted as osteomyelitis involving the upper third of the left tibia, and osteoperforation was performed at Kharkiv Regional Children's Clinical Hospital No. 1 on 17 February 2022. After the beginning of the full-scale invasion of Ukraine, the patient was evacuated to Lviv on 7 March 2022 and subsequently to the United Kingdom on 13 March 2022 for continuation of diagnostic assessment and specialized oncological care. On 16 March 2022, a biopsy of the proximal left tibia was performed. Histopathological and molecular analyses confirmed the diagnosis of Ewing sarcoma, with detection of EWSR1 gene rearrangement by FISH.

The available primary documentation was very limited. Therefore, reliable source data on the exact initial stage, presence or absence of metastases at diagnosis, full results of primary staging, and detailed morphological or immunohistochemical tumor characteristics were not available for analysis. The accessible records indicate the primary localization in the proximal left tibia/left lower limb and molecular

confirmation of EWSR1 rearrangement, but do not allow a full retrospective assessment of baseline relapse risk.

The patient received systemic therapy according to the Euro-Ewing 2012 protocol [16] from 1 April to 1 November 2022, including six cycles of vincristine, doxorubicin, and cyclophosphamide (VDC) and six cycles of ifosfamide and etoposide (IE). Surgical treatment was performed on 16 August 2022 in the form of left transfemoral amputation due to the extent of the primary tumor and the need to achieve local control. The patient completed multimodal treatment and achieved complete clinical remission.

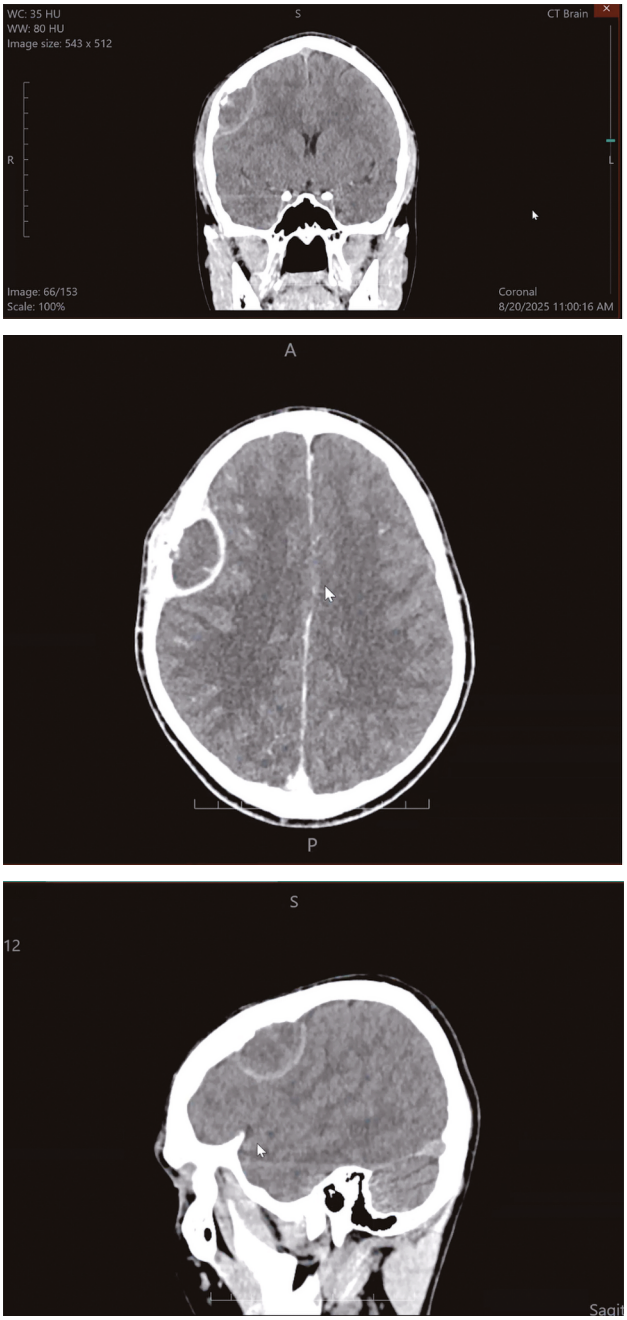

Figure 1. Cranial CT, coronal, axial, and sagittal planes. Osteolytic lesion of the right parietal bone with cortical destruction, extraosseous soft-tissue component, and intracranial extension

The remission period lasted 2 years and 9 months. According to the patient's mother, regular surveillance examinations during remission were not performed.

In August 2025, the patient was admitted with persistent fever (38–39°C) lasting approximately one month, accompanied by chills and no clear infectious source. Initial diagnostic work-up, including CT of the chest and primary site, revealed no evidence of recurrence or infection. Despite antibiotic therapy, febrile episodes persisted.

During clinical examination, a painless palpable mass approximately 1.5 cm in diameter was identified in the right parietal region. The patient also reported headaches. CT and MRI of the brain demonstrated an osteolytic lesion of the right parietal bone with cortical destruction, a paraosseous soft-tissue component, and intracranial extension with parameningeal involvement.

An incisional biopsy of the lesion was performed. Cytological and histopathological examination confirmed metastatic Ewing sarcoma. Bone marrow aspiration and trephine biopsy from multiple sites showed no evidence of tumour infiltration.

Contrast-enhanced staging CT revealed metastatic disease involving:

- right parietal bone,
- left iliac bone,
- right lung segment S5.

Based on a multidisciplinary tumor board decision, treatment for relapsed Ewing sarcoma was initiated. The patient received second-line chemotherapy with high-dose ifosfamide (15 g/m² over 5 days, 2 cycles). Peripheral blood stem cell mobilization and collection were successfully performed in preparation for high-dose chemotherapy with autologous stem cell rescue.

After two cycles of chemotherapy, follow-up CT demonstrated a partial response according to RECIST 1.1 criteria, with a significant reduction in the size of all measurable lesions:

- parietal lesion decreased from 38×29×45 mm to 23×15×25 mm,
- iliac lesion decreased in size,
- pulmonary lesion reduced from 5×5 mm to 2×2 mm.

Surgical resection of the metastatic lesion of the right parietal bone was performed. Histopathological examination revealed isolated tumor cell elements on the dural surface, with no evidence of tumor at the resection margins (R0 resection), along with reactive changes including hemosiderin deposition and inflammatory infiltration.

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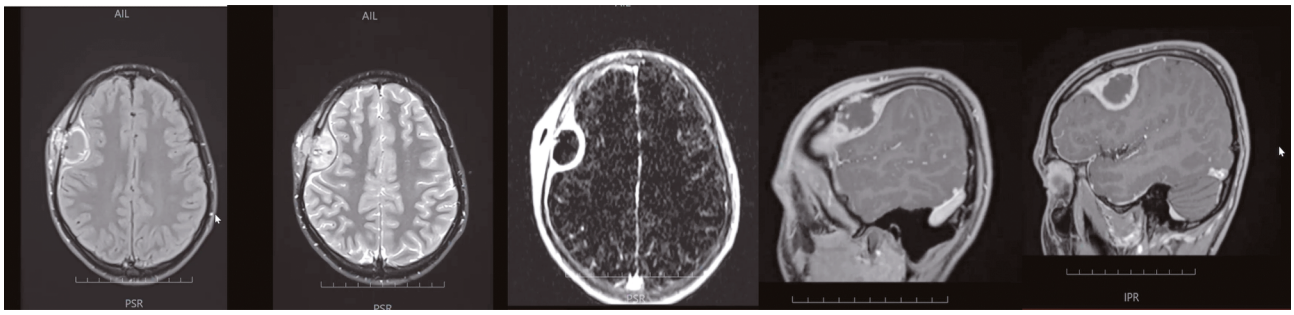

Figure 2. Brain MRI, axial and sagittal planes. Right parietal osteolytic lesion with paraosseous soft-tissue component, intracranial extension, and parameningeal involvement of the frontal and parietal regions

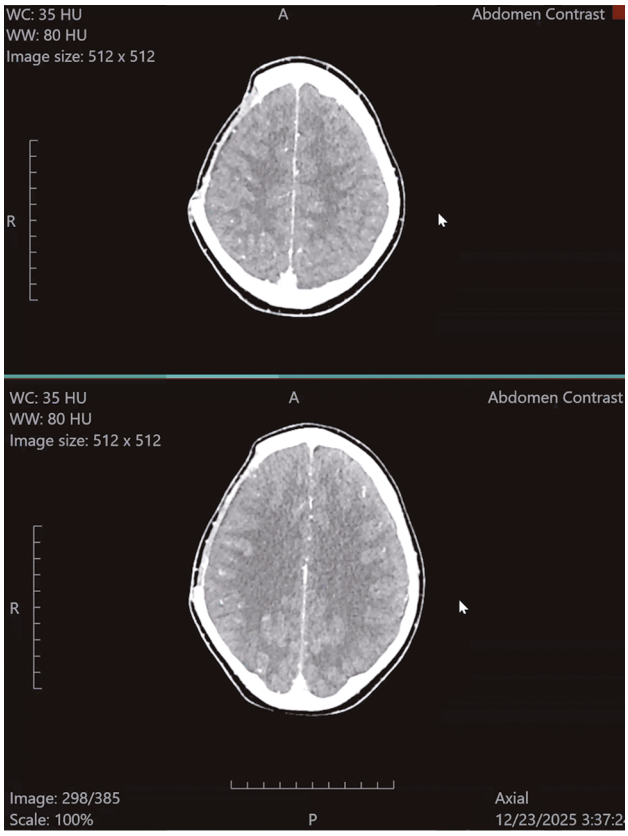

Figure 3. Follow-up contrast-enhanced CT, axial plane. Postoperative changes after resection of the right parietal bone metastasis, without visible residual cranial mass on the presented images

Subsequent imaging demonstrated:

- complete regression of the pulmonary metastasis,
- stabilization of the iliac bone lesion.

The patient proceeded to high-dose chemotherapy (treosulfan and melphalan) followed by autologous stem cell transplantation and was referred for consolidative radiotherapy.

Follow-up and Outcomes

Post-treatment evaluation demonstrated a favorable response to multimodal therapy, including complete regression of the pulmonary metastasis and stable disease in the iliac bone. Surgical management of the cranial metastasis achieved R0 resection, indicating effective local control.

The patient remains under active oncological follow-up with planned:

- radiotherapy to residual metastatic sites,
- maintenance therapy according to high-risk Ewing sarcoma protocols,
- regular imaging surveillance.

Discussion

Ewing sarcoma is a highly aggressive malignant tumor of bone and soft tissue, predominantly affecting children and young adults, with a marked propensity for early dissemination and relapse. Despite advances in multimodal therapy, including systemic chemotherapy, surgery, and radiotherapy, approximately 25% of patients with initially localized disease eventually develop recurrence [1,8]. Although the majority of relapses occur within the first two years, late relapse remains a recognized clinical phenomenon and may present with atypical metastatic patterns, as demonstrated in the present case.

The typical metastatic distribution of ES involves the lungs, bones, and bone marrow. In contrast, intracranial involvement is rare. According to available data, central nervous system (CNS) metastases occur in approximately 6.3% of cases, cranial metastases in around 1%, and skull involvement in up to 9%, with primary skull lesions being more common than metastatic ones [5-7]. The rarity of this localization contributes to diagnostic delay and under-recognition in clinical practice.

The biological behavior of ES is largely driven by the EWSR1-FLI1 fusion protein, which results from the characteristic t(11;22)(q24;q12) translocation and is present in approximately 85% of cases [1]. This oncogenic transcription factor plays a central role in tumor progression by regulating proliferation, differentiation, and metastatic potential. Importantly, intratumoral heterogeneity is influenced by variable expression of EWSR1-FLI1: high expression is associated with a proliferative, undifferentiated phenotype, whereas lower expression promotes

mesenchymal characteristics and increased migratory capacity [10-12]. One of the mechanisms underlying this process involves the regulation of the actin cytoskeleton, which facilitates cellular motility and metastatic dissemination [13].

Metastatic spread in ES follows a multistep cascade including local invasion, intravasation into the bloodstream, extravasation at distant sites, and colonization [4]. This dynamic process, combined with tumor cell plasticity, may explain the occurrence of metastases in unusual anatomical locations, including the skull and intracranial compartment.

From a clinical perspective, intracranial involvement in ES presents a diagnostic challenge due to its nonspecific and often subtle symptomatology. Patients may present with headache, seizures, behavioral changes, focal neurological signs, cranial masses, or remain minimally symptomatic, which can delay diagnosis [9,14]. In the presented case, relapse initially manifested as persistent fever without an identifiable source, followed by a painless parietal mass and headache, further complicating early recognition and highlighting the need to consider metastatic relapse when unexplained systemic or cranial symptoms develop in long-term survivors.

Historically, prophylactic CNS irradiation and intrathecal chemotherapy were explored in an attempt to prevent brain metastases. However, these strategies did not demonstrate a reduction in CNS relapse rates and are no longer included in contemporary treatment protocols [14]. Current management relies on risk-adapted multimodal therapy, with salvage regimens including high-dose chemotherapy and autologous stem cell transplantation in selected patients.

A major clinical issue highlighted by this case is the limited standardization of follow-up strategies for ES survivors. Existing recommendations generally focus on imaging of the primary tumor site and chest to detect local recurrence and pulmonary metastases, especially during the first years after treatment [9,15]. Routine neuroimaging is not included in standard follow-up algorithms, which is reasonable given the rarity of intracranial involvement and the lack of prospective evidence supporting universal brain MRI screening.

Given the possibility of late relapse and rare metastatic localizations, a purely standardized approach may be insufficient for selected patients. However, the findings of this case should not be interpreted as evidence for routine brain MRI in all ES survivors. A more cautious and clinically justified approach is to consider brain MRI in patients with neurological symptoms, cranial complaints, palpable cranial lesions, atypical persistent fever without an identifiable source, disseminated relapse, or other high-risk features. Further prospective studies are required to define which patients may benefit from selective neuroimaging and to avoid unnecessary investigations in low-risk, asymptomatic survivors.

Conclusions

This case report demonstrates that Ewing sarcoma may relapse after a prolonged remission period with a rare skull metastasis and intracranial extension. The presentation should be interpreted as metastatic relapse rather than local recurrence, because systemic staging revealed lesions in the right parietal bone, left iliac bone, and segment S5 of the right lung. The nonspecific onset with persistent fever, followed by the appearance of a painless parietal mass and headache, emphasizes the importance of careful clinical assessment of atypical symptoms in long-term survivors. Multimodal salvage treatment, including high-dose ifosfamide, surgical resection, high-dose chemotherapy with autologous stem cell transplantation, and planned radiotherapy, achieved favorable early disease control. The case highlights a gap in current post-remission surveillance strategies, which generally prioritize the primary tumor site and chest imaging but do not routinely include neuroimaging. Brain MRI may be considered in selected patients with neurological symptoms, cranial complaints, unexplained fever, disseminated relapse, or other high-risk features; nevertheless, standardized recommendations require further prospective evidence.

Article Declarations

Raw Data and Materials. The raw data and materials supporting the findings of this study are available from the corresponding author upon reasonable request.

Study Limitations. This case report has several limitations. First, it represents a single clinical observation, which limits the generalizability of the findings. Second, primary diagnostic documentation was incomplete because the patient was evacuated from Kharkiv to Lviv and then to the United Kingdom after the beginning of the full-scale invasion of Ukraine. As a result, the exact initial stage, complete primary staging results, and detailed morphological and immunohistochemical tumor characteristics could not be reliably reconstructed.

Third, molecular characterization beyond confirmation of EWSR1 rearrangement was not extensively available, which restricts deeper analysis of tumor biology and its potential role in metastatic behavior. The absence of standardized follow-up data during the remission period also limits the ability to fully assess the dynamics and timing of relapse development.

Finally, given the rarity of intracranial involvement in Ewing sarcoma, conclusions regarding selective neuroimaging and optimal surveillance strategies remain hypothesis-generating and require validation in larger, prospective studies.

Funding. The study received no external funding.

Ethics Approval Statement. According to Protocol No. 17 of the meeting of the Department of Oncology, Bogomolets National Medical University, this work did not require review by the ethics committee because all requirements for the protection of the patient's personal data were met. The manuscript contains no directly identifiable patient information. Written informed consent was obtained from the patient's legal representative for the processing of personal data and publication of anonymized clinical information and images.

Conflict of Interest. The authors declare no conflict of interest. Written informed consent was obtained from the patient's legal representative for publication of this case report, including anonymized clinical data and accompanying images. All authors have read and approved the final manuscript.

AI Statement. The authors used OpenAI, San Francisco, CA, USA for language editing according to journal requirements. The authors reviewed and verified all AI-assisted content to ensure accuracy, integrity, and compliance with ethical standards. AI tools were not used to generate research data, interpret clinical findings, or make diagnostic or therapeutic decisions.

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Метастатичний рецидив саркоми Юїнга з ураженням тім'яної кістки та інтракраніальним поширенням після лікування за протоколом Euro-Ewing 2012 і лівобічної трансфеморальної ампутації

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Анотація. *Вступ.* Саркома Юїнга є високоагресивною злоякісною пухлиною кісток, що характеризується високим ризиком рецидиву та метастатичного поширення, тоді як ураження кісток черепа й інтракраніальне поширення залишаються рідкісними та клінічно складними проявами.
Мета. Метою цієї публікації є представлення випадку пізнього метастатичного рецидиву саркоми Юїнга з метастазом у правій тім'яній кістці та інтракраніальним поширенням через 2,9 року після завершення лікування за протоколом Euro-Ewing 2012 і лівобічної трансфеморальної ампутації, а також обговорення значення цього випадку для індивідуалізованого післяремісійного спостереження.
Матеріали та методи. У 11-річного пацієнта після мультимодального лікування було досягнуто повної клінічної ремісії; однак через евакуацію та подальше лікування за кордоном після початку повномасштабного вторгнення в Україну первинна медична документація була обмеженою, а регулярне візуалізаційне спостереження в період ремісії, за наявним анамнезом, не проводилося. У серпні 2025 року пацієнта госпіталізували з персистуючою гарячкою без встановленого інфекційного джерела; згодом з'явилися безболісне утворення в правій тім'яній ділянці та головний біль. КТ і МРТ головного мозку виявили остеолітичне ураження правої тім'яної кістки з параосальним м'якотканинним компонентом та інтракраніальним параменінгеальним поширенням, а гістопатологічне дослідження підтвердило метастатичну саркому Юїнга.
Результати. Стадіювання виявило додаткові метастатичні ураження лівої клубової кістки та сегмента S5 правої легені. Друга лінія лікування включала високодозову хіміотерапію іфосфамідом, мобілізацію та забір периферичних гемопоетичних стовбурових клітин, хірургічну резекцію краніального метастазу й високодозову хіміотерапію з автологічною трансплантацією стовбурових клітин із подальшим скеруванням на консолідуючу променеву терапію. Після двох циклів хіміотерапії досягнуто часткової відповіді за критеріями RECIST 1.1; надалі спостерігали повну регресію легеневого метастазу та стабілізацію ураження клубової кістки.
Висновки. Цей випадок демонструє можливість пізнього метастатичного рецидиву саркоми Юїнга з нетиповою краніальною та інтракраніальною локалізацією і підкреслює обмеження стратегій спостереження, які переважно зосереджені на первинній ділянці та органах грудної клітки. МРТ головного мозку не слід розглядати як універсальну рутинну вимогу для всіх пацієнтів у ремісії, однак її застосування може бути доцільним у пацієнтів із неврологічними симптомами, краніальними скаргами, незрозумілою персистуючою гарячкою або іншими високоризиковими клінічними ознаками. Стандартизовані показання до нейровізуалізації потребують подальшого вивчення.

Ключові слова: саркома Юїнга, метастазування новоутворення, новоутворення черепа, новоутворення головного мозку, магнітно-резонансна томографія, іфосфамід, трансплантація гемопоетичних стовбурових клітин.

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