Oncology Research and Treatment

Novel Insights from Clinical Practice

Oncol Res Treat 2018;41:135–138
DOI: 10.1159/000485626

Received: September 12, 2017
Accepted: November 22, 2017
Published online: February 27, 2018

Metachronous Spontaneous Remission of Melanoma Lung Metastasis and Mediastinal Lymph Node Metastases

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Established Facts

- Spontaneous remissions are rare but valid events in malignancies and in the past have led to the development of mainstay oncologic therapies.
- Spontaneous regression of melanoma metastases occurs in approximately 1 out of 400 patients. Most reports refer to nodal metastases, but long-lasting remissions of advanced visceral metastases are also documented.

Novel Insights

- This case report presents a rare spontaneous complete regression of a solitary pulmonary melanoma metastasis. Subsequently, concurrent mediastinal nodal metastases progressed before later also showing spontaneous regression.
- It is felt that microenvironmental immune response plays an essential role in spontaneous melanoma remission and thus deserves a more systematic research with a view to discovering novel treatment options.

Keywords

Melanoma · Cancer · Spontaneous remission · Regression · Immune response

Summary

Background: Spontaneous remissions are rare but valid events in malignancies and in the past have led to the development of mainstay oncologic therapies. **Case Report:** We present a rare case of spontaneous regression of a solitary pulmonary melanoma metastasis with complete remission persisting for 28 months. Concurrent mediastinal nodal metastases progressed at the time of remission of the lung metastasis, but also demonstrated regression in follow-up fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) imaging. Metastatic nodes showed only minimal residual metabolic activity after 38 months of follow-up from the appearance of metastatic disease. **Conclusion:** This case report presents a rare spontaneous complete regression of a solitary pulmonary melanoma metastasis. Biological pathways involved in spontaneous regression in cancer are discussed.

Introduction

Spontaneous remission (SR) refers to the complete or partial, temporary or permanent disappearance of all or at least relevant parameters of a verifiably diagnosed malignant disease without any medical treatment or in the presence of therapy which is considered inadequate to produce the resulting regression [1]. Regressions should persist at least 1 month and should exceed waxing and waning of stable disease. SR as a rare but valid and paradigmatic phenomenon was already highlighted in a key note lecture at the

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1st International Cancer Conference in 1906 [2]. Modern oncology owes some of its therapeutic mainstays and innovative research areas to observations of SR: endocrine therapy, immunotherapy, anti-angiogenesis, and virus-based experimental treatments. In recent years, discussions on SR have been stoked by the substantial cancer overdiagnosis in screening programs [3]. The frequency of SR in cancer is most often cited in the medical literature as 1: 60.000–100.000, which is based on an obsolete estimate. A newer perspective is more revealing: Very few reports of SR in cancers of the lung, colon, or pancreas suggest a prevalence of < 1:1,000,000 in these frequent types of cancer. However, SR in indolent malignant lymphoma or in metastatic renal cell carcinoma occur in at least 1 out of 100 patients [4–7], and the frequency of SR in hepatocellular cancer was calculated to be 0.4% [8]. SR in non-*MYCN* amplified neuroblastoma IVS is observed in about 80% of young patients [9]. SR of malignant melanoma (MM) metastases reportedly occurs in 1 out of 400 patients [10]. This dramatic epidemiological variation of cancer types and SR incidence suggests specific biological characteristics in the onset of SR.

Case Report

In November 2012, the second author (G.E., Professor of Medicine and former Head of a Department of Surgery) arranged the excision of a suspicious mole on his left forearm, which had turned into an ulcerating raisin-like lesion over a 6-week period. Histopathology confirmed superficial spreading MM. Tumor thickness was 1.9 mm, Clark level IV, 2 mitoses/mm^2. There was a dense focal infiltration of lymphocytes peripheral to the melanocytic tumor. Unfortunately, those lymphocytes were not immunotyped. Because of initial inadequate (< 1 mm) margins, a wide local excision was performed 2 weeks later. When complete staging (chest X-ray, bone scan, positron emission tomography-computed tomography (PET-CT), sentinel lymph node dissection) did not reveal any evidence of malignant dissemination, the stage was T2b N0 M0, UICC Stage IIA, CL IV. In June 2014, 19 months after the original biopsy, a chest-X-ray was performed due to thoracic pain, which demonstrated a 12-mm round lesion suspicious for metastasis in segment 4 of the right lung. Pathological glucose uptake in fluorodeoxyglucose (FDG)-PET/CT imaging corroborated this diagnosis. Additional intensive FDG enhancement was detected in mediastinal lymph nodes L7, while ambiguous tracer enhancement was present in mediastinal lymph node L4R. A transbronchial biopsy (June 2014) confirmed metastatic MM in mediastinal lymph node L7. Tumor board recommendation for this 83-years old patient initially was best supportive care. When later molecular pathology of the metastatic node revealed *BRAF*-464–469 mutation and *NRAS* wild type, specific oncological treatment in a University Cancer Center was offered. Considering a potential survival benefit of only a few months, the patient declined treatment and settled his affairs. In April 2015, chest radiography carried out because of transient thoracic pain showed distinct mediastinal enlargement. A chest CT scan indicated progressive mediastinal metastases with infracarinal nodes now measuring up to 74 × 44 mm and pretracheal lymph nodes up to 44 mm in diameter. However, there was no longer any evidence of the pulmonary node. Restaging in July 2016 with whole body PET-CT confirmed persistent absence of the lung lesion, while mediastinal lymphadenopathy remained stable in size with infracarinal lymph nodes measuring 75 × 39 mm and now showing an inhomogeneous glucose uptake consistent with central necrosis. Lymph nodes of segments L4R and L2 remained enlarged but demonstrated just a discrete tracer uptake. In August 2017, the now 86-year old man remained quite active with a remarkable ECOG 0 performance status without undergoing any conventional or unconventional oncological therapy. PET-CT restaging on August 24, 2017 did not reveal any relapse of pulmonary metastasis, and there was a distinct shrinkage of the former metastatic mediastinal mass which now did not show any FDG uptake (fig. 1). Lymph node 4R still presented with suspicious FDG uptake.

The patient as co-author fully consented to this publication.

Discussion

In MM, partial spontaneous regression of the primary lesion is not uncommon, occurring in 10–35% regardless of tumor thickness and in thin MM with less than 1-mm thickness in even up to 61% [10]. Clinically, partial regression is mainly characterized by whitish and grayish areas of pigmentation. Histopathologically, the process starts with a dense infiltrate of lymphocytes and ends with fibrosis and/or melanosis within a thickened papillary dermis [11]. Recent studies cast doubt on the potential negative prognostic implication of partially regressive MM primary lesions and suggested a protective effect [12].

Complete regression of MM primary is more rare: Studying nearly 140,000 patients with MM, Kamposioras et al. [13] found 3.2% metastatic MM of unknown primary (MUP) suggesting complete SR of the primary. In a matched controls study, Lee et al. [14] established a survival advantage for patients with stage III/IV MUP, indicating a positive prognostic impact of complete regression of the MM primary. As for SR of metastatic MM, about 100 case reports can be found in the medical literature taking into account the review by Kalialis et al. [15] and more recent publications. Most reports refer to partial or complete SR of metastatic cutaneous or nodal lesions. However, there are well documented cases of long-lasting (> 5 years) complete SR of widespread visceral and even cerebral metastases of MM [16–18].

SR in cancer represents a heterogeneous phenomenon with apparently different biological pathways finally resulting in apoptosis or differentiation in malignant cells. Endocrine changes, febrile infections, intrinsically or extrinsically triggered anti-angiogenesis, senescence mediated by telemerase inhibition, nutritional or metabolic factors, and ending exposure to carcinogens have been linked to SR in different types of malignancy [4, 19]. A crucial role of antitumor immune response is evidenced by SR after vaccination, withdrawal of immunosuppressants, or in patients with acquired immune deficiency syndrome (AIDS) following improved immunity [19, 20].

More than any other type of cancer, MM is considered as a model tumor for immuno-oncology [21]. A strongly positive delayed hypersensitivity response to allogenic melanoma antigens and lymphocytic infiltration have been reported early on in MM patients with SR [17, 22]. More recently, this cellular immune response could be linked with less CD4+ T cells than CD8+ cytotoxic T lymphocytes and apparently is fostered by an immunopermissive microenvironment with a low number of FOXP3+CD4+ regulatory T cells [10, 23]. Vitiligo frequently associated with response to immunotherapy of MM but also with SR is considered as a sign of good prognosis, and biopsy specimens of vitiligo also show nearly exclusively CD8+ lymphocytic infiltrates [24].

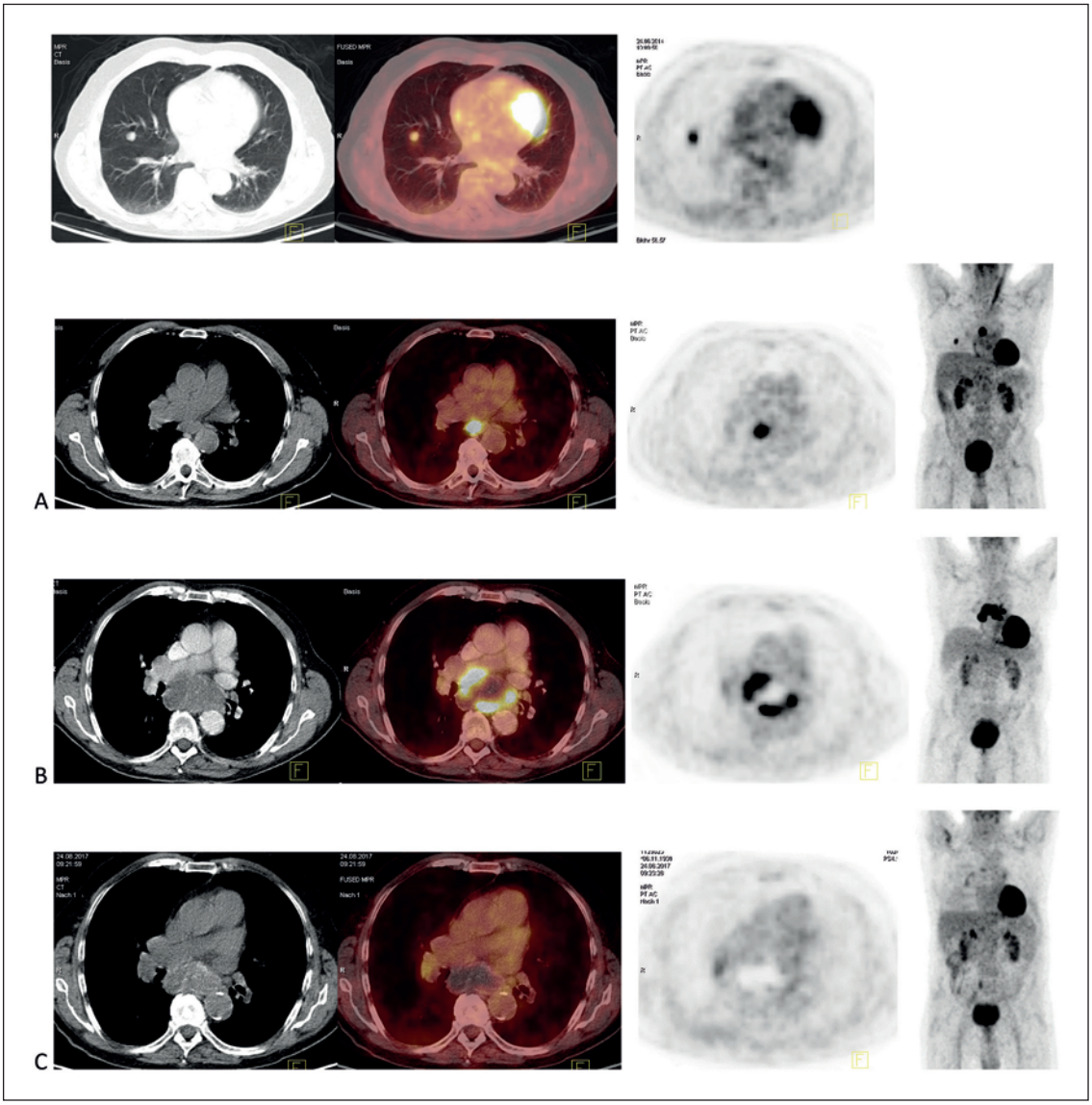

Fig. 1. Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT: **A** June 24, 2014: metastatic node in right lung and mediastinal lymph node metastases; **B** July 21, 2016; **C** August 24, 2017.

A gene signature of a high-immune response type in metastatic MM before treatment is correlated with brisk tumor-infiltrating CD3+ lymphocytes and better survival [25]. Similarly, in a porcine model, SR of MM was paralleled by a significant upregulation of genes related to immune response. Histologically, immune response consisted of infiltrates of less CD4+ than CD8+ T cells, suggesting a cytotoxic lymphocyte response, whereas neither natural killer cells nor senescence or differentiation seemed to play a role in regression [26]. However, SR in MM is not conclusively explained by immune response pathways which are tapped in modern checkpoint blocking therapies: Moreira et al. [27] reported a patient with SR of metastatic MM and findings of T-cell-mediated immune response who had progressed under ipilumumab treatment 2 years before.

This case of complete SR of a solitary lung metastasis from MM 10 months after detection of concurrent pulmonary and mediastinal tumor spread is remarkable. Tran et al. [19] found only 11 cases of SR of lung metastases in MM up to 2013. In our patient, no histopathological examination of the lung lesion was performed. However, histopathological confirmation of mediastinal nodal metastatic spread and PET-CT imaging were very convincing of lung metastasis. Noteworthy in this case was the substantial progression of mediastinal nodal metastases at the time of complete SR of the pulmonary metastasis. 15 months later, mediastinal lymphadenopathy remained stable in size with metabolic evidence of central necrosis. Further regression could be observed another 13 months later. 38 months after histopathological confirmation of metastatic disease, there is no evidence of active malignancy in the absence of any conventional or unconventional oncological therapy, even without complete SR of the nodal metastases. In metastatic MM, median overall survival used to be about 8 months but has increasing to over 2 years owing to both anti-PD-1-based therapy and combined BRAF and MEK inhibition [28, 29]. In our patient, metachronous remission and brisk lymphocytic infiltrates of the primary suggest microenvironmental immune factors to be involved in regression. Nevertheless, in view of an often decreased

immune activity in older age and the more focal and pertitumoral type of lymphocytic infiltration in this patient, other processes leading to regression like telomerase shortening cannot be ruled out.

The incidence of MM in Germany has increased by 700% between 1970 and 2008 and is expected to double further within a few decades [29]. Expenditures for state-of-the-art palliative therapy of metastatic MM with inhibitors of BRAF-RAS-MEK signaling and/or checkpoint inhibitors may far exceed €/$100,000 for a single patient. Given the increasing incidence of MM, a systematic study of SR is feasible and may lead to cost-effective innovative treatment strategies, especially as research findings in the melanoma model are potentially transferable to other types of cancer [21]. Thus, Jose Basalgia's [30] statement applies in terms of meticulous scrutiny of cases of SR: '*So in the era of genomic medicine a single case (n of 1) could be far more valuable than some large clinical trial. For those in the oncological community who are clinicians at heart, welcome back, we need you.*'

Acknowledgment

We kindly thank Prof. Dr. Dr. Wolfgang Schäfer, Dept. of Nuclear Medicine, Maria-Hilf-Kliniken Mönchengladbach for providing the PET-CT images, and William M. Buchholz, MD, Hematologist & Oncologist, Mountain View, CA, USA for comments and language editing.

Disclosure Statement

Both authors deny any conflicts of interest.

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