Spontaneous Regression of Melanoma Metastases Associated with a Flare of Eczema

Shevya M Tiwari¹*, Alex Powell², Jason M Dyke³

¹ Sir Charles Gairdner Hospital, Perth, Australia
² Department of Oncology, Hollywood Private Hospital, Perth, Australia
³ Department of Anatomical Pathology, Sir Charles Gairdner Hospital, Perth, Australia, St John of God Pathology, Subiaco, Suite 204, Level 2 Cambridge St, Subiaco, Australia

Abstract

Introduction: Spontaneous regression of metastatic melanoma is a rare event with only a handful of cases documented in the world literature. The phenomenon remains much of an enigma however there is an increasing body of evidence to support an immunologic basis to regression.

Presentation of case: We report a case of spontaneous regression of widespread metastatic melanoma diagnosed radiologically in a 54 year old otherwise well Caucasian woman. Regression of metastatic disease was first noted when the patient presented with a severe flare of otherwise well controlled atopic eczema. This continued to complete regression of all metastatic disease over a period of 26 months. She remained clinically well and disease free for three years, however subsequently developed new pulmonary nodules on routine PET scan suggestive of new metastases.

Conclusion: We discuss mechanisms of regression and hypothesize that this patient’s flare of eczema was related to T cell hyperactivity induced by tumour-associated-antigens produced by melanoma cells. Cases of tumour regression and research into pathways involved in regression may offer insight into novel treatment options.

Keywords: Spontaneous regression; Metastatic melanoma; Immune sensitisation

Received: June 18, 2014; Accepted: September 6, 2014; Published: November 2, 2014

Competing Interests: The authors have declared that no competing interests exist.

Copyright: 2014 Tiwari SM et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

*Correspondence to: Shevya M Tiwari, SirCharlesGairdnerHospital, Perth, Australia; Email: shevya.tiwari@health.wa.gov.au
Introduction

Spontaneous regression refers to the partial or complete disappearance of a malignant tumour in the absence of all treatment considered capable of producing regression. It is a rare but well documented event in the literature, with the phenomenon seen in melanomas as well as neuroblastomas and renal cell carcinomas [1, 2]. While regression is recognised to be part of the natural history of some melanomas, with 18.5-50% of primary tumours showing partial or complete histopathological regression [1], spontaneous regression of metastatic melanoma is much rarer with an estimated incidence of 0.22-0.27% [1]. The mechanisms are largely unknown but current research suggests the involvement of a T-cell mediated anti-tumour response [2]. We report a case of spontaneous regression of metastatic melanoma with widespread radiologically diagnosed metastases, in association with a flare of eczema.

Case report

A 54 year old otherwise well Caucasian woman presented with a five millimetre brown papule overlying the dorsum of her left foot in January 2007. A suspected dermatofibroma, the lesion was excised with close margins. Histopathology revealed a Clark level IV nodular malignant melanoma, with a Breslow thickness of 1.28mm. Wide local excision and sentinel lymph node biopsy demonstrated one of two sentinel nodes involved, with morphological resemblance of the metastasis to the cutaneous primary (Figure 1). The metastatic malignant cells displayed strong S100 positivity. Left inguinal block resection revealed no further nodal metastases. PET scan showed no evidence of residual or metastatic disease and she was commenced on a course of adjuvant Interferon. Immunotherapy options were not available at this time and the patient did not trial alternative therapies.

After completing twelve months of Interferon, routine PET scan in 2008 revealed multiple foci of metastatic nodal disease in the abdomen and pelvis as well as diffuse splenic and skeletal infiltration (Figure 2A). CT confirmed extensive hilar and mediastinal lymphadenopathy as well as numerous small...
peripheral lung nodules consistent with metastatic disease. The patient refused further investigation and therefore tissue diagnosis of metastatic disease was unable to be confirmed.

**Figure 2 Left:** PET scan 2008. Radiological appearances in keeping with widespread metastatic melanoma. Extensive FDG (fluorodeoxyglucose) uptake noted in the gastrocnemii; diffuse infiltration within the spleen, spine, pelvis and ribs; nodal disease in the infraclavicular, mediastinal and perihilar regions as well as within the portahepatis nodes and upper abdominal para-aortic nodes. **Right:** PET scan 2013. Regression of previously seen metastatic disease. Three new peripheral lung nodules with radiological appearances suggestive of metastatic disease were noted in this study; one nodule visible on this image.

Six months later, she presented to her oncologist and was noted to be suffering from a severe, widespread flare of atopic eczema which had previously been mild and well controlled with emollient regimens. Repeat CT revealed partial regression of the right hilar lymph nodes with stable disease elsewhere. She was referred to a dermatologist who commenced a short course of oral and topical steroids with improvement in her eczema.

Six monthly chest X-rays and yearly CT scans showed continual regression and twenty six months later, there was no evidence of any metastatic disease. Three years later, a repeat PET scan confirmed complete resolution of initially detected disease, however three new pulmonary nodules were present with appearances suggestive of new metastases (Figure 2B). She has remained clinically well and has persisted in her request to not have further invasive investigation or active treatment for melanoma.

**Discussion**

Reported cases of regression in metastatic melanoma are almost all in response to an inflammatory or immune sensitising stimulus [1-3]. Melanoma is responsible for the production of numerous tumour associated antigens (TAA) capable of inducing tumour-directed immune responses and representing potential immunotherapy targets [4]. This immune response takes the form of, amongst others, increased numbers of CD4+ tumour infiltrating T lymphocytes, cytotoxic T lymphocytes (CTL’s) and activated dendritic cells [2, 5, 6]. Various potential stimuli have been cited in publications as possibly resulting in this immune activation in melanoma patients[1, 3] and the TAA’s themselves may play a role in this process in a subset of patients [2, 4].
It would seem in this case that the flare of the patient’s previously well controlled eczema was either causally linked to the occurrence of regression, or a cutaneous manifestation of systemic immune sensitisation to the metastatic disease. The patient did not have a history of autoimmune disease and had ceased the use of melanoma-specific treatment for four months prior to presentation with the flare of eczema. We hypothesise that this patient’s severe flare of eczema was related to T cell hyperactivity resulting from immune system stimulation by melanoma TAA’s.

The likely recurrence of the patient’s metastatic disease with the appearance of new pulmonary nodules on chest imaging after apparent complete resolution suggests a form of ‘immunosculpting’ by the malignant cells. This involves the development of immune-avoidance techniques by the melanoma cells, allowing them to escape immune destruction by CTL’s[4]. This is a similar mechanism to that by which metastatic melanoma develops resistance to immunotherapy agents [7].

There are limited studies looking at the histopathology and immunology behind the regression of metastases from melanoma, perhaps due to the low incidence of the phenomenon. There is however an increasing body of evidence supporting an immunological basis to the regression of cutaneous tumours, indirectly evidenced by increased numbers of CD4+ T lymphocytes admixed with residual malignant cells in cutaneous melanomas demonstrating some form of regression. Modern immunotherapies targeting this immunogenic process, including Interleukin-2, ipilimumab and more recently the anti-programmed cell death protein 1 (PD-1) antibodies nivolumab and lambrolizumab, are relatively recent advances in the treatment of metastatic melanoma [8, 9]. There is still much need for the development of safer and more efficacious immunotherapies, which are likely to become the dominant treatment modality in the future management of metastatic melanoma.

**Conclusion**

Spontaneous regression of metastatic cancer remains a rare event and is seen in only a few tumour types, including melanoma. We report a case of regression of widely metastatic malignant melanoma, with initial disease resolution corresponding to a severe eczema flare suggesting an immune-mediated mechanism of regression. We are yet to fully grasp the implications of spontaneous regression of tumours and further evaluation into the exact immunologic mechanisms has the potential to develop novel treatment options for melanoma and other tumour types.

**Abbreviations**

PET – Positron Emission Tomography  
CT – Computed Tomography  
TAA – Tumour Associated Antigens  
CTL – Cytotoxic T Lymphocytes

**Consent**

The patient has given informed consent for the publication of this case report.


