

# Complete Spontaneous Regression of Pulmonary Metastatic Melanoma

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**BACKGROUND.** Complete spontaneous regression of melanoma metastatic to the lungs is a rare event.

**OBJECTIVE.** To report a case of biopsy-proven melanoma metastatic to the lung with complete spontaneous regression.

**METHODS.** Multidisciplinary case report.

**RESULTS.** A 35-year-old white female was diagnosed with metastatic melanoma to the lung. A pleural biopsy confirmed the diagnosis. Partial spontaneous regression was noted by a staging computed tomography scan prior to enrollment in an investigational protocol. Complete spontaneous regression occurred over 5 months without any form of conventional or alternative therapy, and the patient remains disease-free 3 years after diagnosis.

**CONCLUSIONS.** Our case represents the seventh case of complete spontaneous regression of melanoma metastatic to the lung, and the only case with histologic confirmation of both the primary and pulmonary metastatic lesions. The patient was pregnant twice between the time of her initial diagnosis of primary melanoma and pulmonary metastatic disease. © 1998 by the American Society for Dermatologic Surgery, Inc. *Dermatol Surg* 1998;24:915-919.

Spontaneous regression of cancer is defined as "the partial or complete disappearance of a malignant tumor in the absence of all treatment or in the presence of therapy which is considered inadequate to exert a significant influence on neoplastic disease."<sup>1</sup> Spontaneous regression does not necessarily imply cure and need not result in complete disappearance of the tumor. Using these criteria, the spontaneous regression of cancer has been well described and is widely accepted as a rare phenomenon.<sup>1-19</sup>

Partial spontaneous regression of the primary lesion of melanoma is not uncommon, occurring in the range of

3-15% of cases.<sup>5,6,16,18</sup> However, complete spontaneous regression of the primary lesion is rare and complete regression of metastatic lesions even rarer. Partial or complete spontaneous regression of metastatic melanoma most often occurs in cutaneous or nodal lesions.

Herein, we report a case of melanoma metastatic to the lungs with subsequent complete spontaneous regression of the metastatic lesions. This represents the seventh case reported in the English language literature (Medline) and the first with histologic confirmation of the pulmonary metastatic lesions.

## Case Report

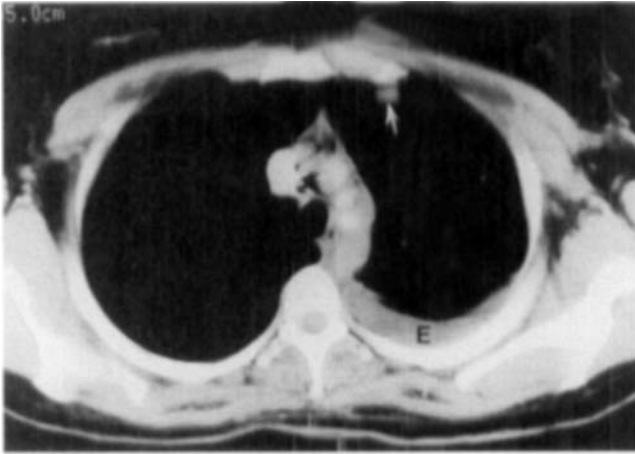
In August 1987, a 29-year-old gravid female noted a darkening lesion on the upper back. Biopsy revealed melanoma, type unclassified, 1.3 mm in Breslow depth extending to the deep margin. The patient underwent wide local excision with 4.0-5.0-cm margins revealing scar and inflammation, and no residual melanoma. No evidence of regional or distant disease was noted based on a thorough history and physical examination. Postpartum, following delivery of a healthy baby in 1988, a chest x-ray (CXR) revealed no abnormality, and abdominal ultrasound showed two hepatic hemangiomas that were stable from previous exams. The placenta was free of melanoma based on histologic and clinical evaluation.

In November 1992, the patient noted a new left axillary mass following the uncomplicated birth of her second child. Staging head and body computerized axial tomography (CT) scans revealed left axillary lymphadenopathy without evidence of additional disease. Open biopsy and subsequent left axillary lymph node dissection revealed one of 16 lymph nodes positive for metastatic melanoma.

In August 1993, the patient noted a new soft tissue nodule in the left axillary dissection scar. Fine needle aspirate was positive for recurrent melanoma. Head and body CT scans demonstrated a tiny left upper lobe lung nodule that was too small to characterize and were

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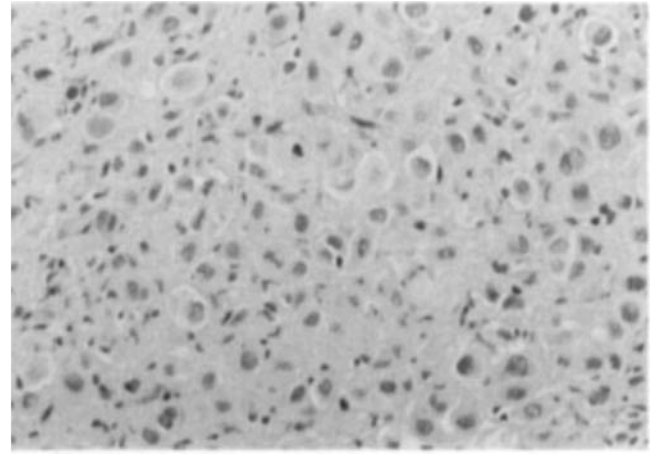
**Figure 1.** Contrast enhanced chest CT demonstrates a left upper lobe lung nodule (arrow), mediastinal lymph node enlargement, and a left pleural effusion (E).

otherwise unremarkable. Wide local excision of the soft tissue recurrent disease was performed.

In November 1993, the patient complained of increasing left-sided chest pain with pain on inspiration. Staging head and body CT scans demonstrated a moderate sized left pleural effusion, a 1.5-cm left upper lobe lung nodule, left upper mediastinal, left internal mammary, and aorto-pulmonary window lymph node enlargement, and a 5 × 6 × 3-cm mass contiguous with the gastroesophageal junction and the descending thoracic aorta (Figures 1 and 2). A pleural tap for cytology was negative for neoplasm with numerous reactive mesothelial cells. A CT-guided pleural biopsy was then performed revealing metastatic melanoma to the lungs (Figures 3 and 4). The pleural biopsy was complicated by a small pneumothorax that subsequently resolved.

In December 1993, the patient elected to enroll in an investigational protocol for stage IV melanoma. Prior to therapy, repeat head and body CT scans demonstrated

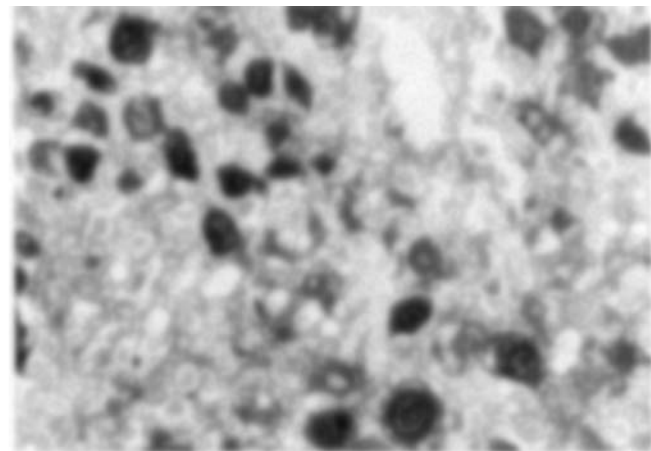
**Figure 2.** Contrast enhanced CT demonstrates a mass (M) contiguous with the gastroesophageal (GE) junction.

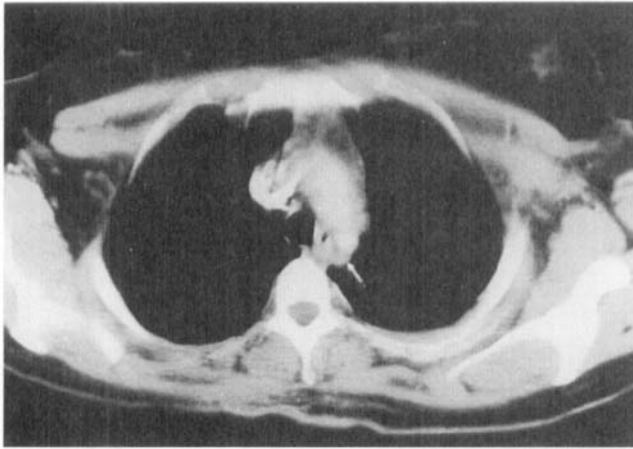


**Figure 3.** Pleural core biopsy demonstrates atypical epithelioid cells compatible with metastatic melanoma (H&E, ×200).

a marked reduction in the size of the left pleural effusion and mediastinal lymph node enlargement with complete resolution of the left upper lobe lung nodule (Figure 5) with no other evidence of distant disease. The residual posterior mediastinal mass now measured 4 × 4 × 1.5 cm (Figure 6). Because of the observed improvement in the absence of treatment, the patient was not enrolled into the protocol. Follow-up CT scans in February 1994 showed continued improvement. A complete response with no evidence of disease was noted on chest CT scan in May 1994 (Figure 7). No further therapy was instituted and the patient remains free of disease 9 years after the initial diagnosis of melanoma and 4.5 years after the diagnosis of metastatic disease. The most recent CT scan in October 1996 and CXR in January 1997 demonstrated no evidence of recurrence. To date the patient has received no systemic therapy for her disease. Of note, specific detailed questioning revealed no change in diet, lifestyle, activity, or "alternative therapy."

**Figure 4.** S100 protein immunoperoxidase stain decorates the atypical malignant cells confirming a diagnosis of metastatic melanoma (×400).



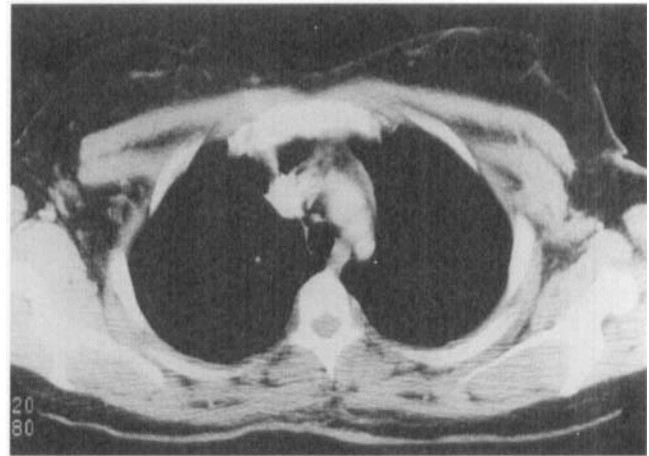
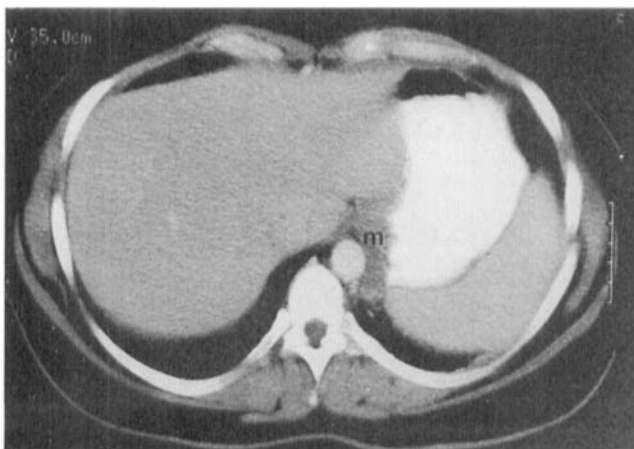


**Figure 5.** Spontaneous regression of left upper lobe lung nodule with minimal residual mediastinal lymph node enlargement (arrow) is noted on this follow up chest CT obtained 1 month later. Note also improvement in left pleural effusion.

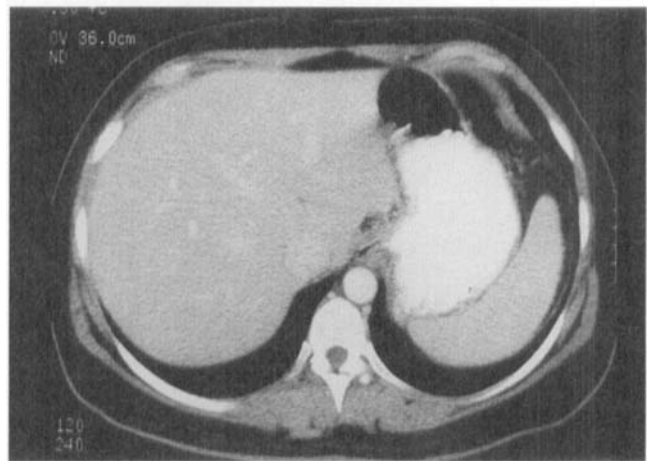
### Discussion

Spontaneous regression of metastatic melanoma is a rare event, reported as occurring in approximately 0.22–0.27% of cases.<sup>4,9,12,16,17</sup> The complete spontaneous regression of metastatic melanoma was first reported in 1889 by Bennett.<sup>3</sup> In 1979, Bodurtha reviewed 29 cases of spontaneous regression in metastatic melanoma.<sup>2,4</sup> Of these, 26 had regression of cutaneous and/or lymphatic nodal metastases and five had regression of radiographically demonstrated pulmonary metastases. In 1986, Mikhail and Gorsulowsky reported one additional case of spontaneous regression of metastatic melanoma to the lungs.<sup>12</sup> The present case represents the seventh report of complete spontaneous regression of melanoma with metastasis to the lungs and the first in the English language literature with histologic confirmation of pulmonary involvement (Medline). When evaluating cases of spontaneous regression in meta-

**Figure 6.** Mass (m) contiguous with GE junction is also smaller.



A



B

**Figure 7.** Complete resolution of left pleural effusion, mediastinal lymph node enlargement and mass contiguous with GE junction respectively is noted on this follow up CT obtained approximately 5 months after CT demonstrating metastatic disease.

static melanoma, histologic confirmation of the suspected lesion may be important due to the fact that open thoracotomy on patients with melanoma and radiographic lesions suspicious for pulmonary metastasis shows benign or unrelated disease in nearly one-third of cases.<sup>20</sup>

The single most important predictor of prognosis and risk of metastasis is the primary tumor thickness measured in millimeters (Breslow depth).<sup>21</sup> While melanoma can metastasize to any organ, the most common sites of metastasis are the skin and subcutaneous tissue and lymph nodes.<sup>21</sup> The most common visceral sites of metastasis are, in order of decreasing frequency, the lung, liver, brain, bone, and gastrointestinal tract.<sup>22-24</sup> Given the relative frequency of pulmonary metastatic melanoma, the occurrence of spontaneous regression in these lesions based on reports in the literature must be rare indeed. Patients with pulmonary metastasis have

an overall 5-year survival of approximately 4% and a median life expectancy of 6-7 months.<sup>25</sup>

A number of observations have stimulated interest in the role of pregnancy and melanoma. While controversial, most studies regarding prognosis of pregnancy-associated melanoma suggest a possible decreased disease-free interval but no effect on overall survival when controlling for tumor thickness and stage of disease.<sup>26-34</sup> A waiting time of 0-5 years to become pregnant after the diagnosis of melanoma is recommended depending on tumor thickness, stage of disease, patient age, and desire to get pregnant. Definitive answers to how pregnancy affects melanoma, if at all, remain unclear.

The mechanisms involved in the spontaneous regression of primary and metastatic melanoma are unknown but may be related to immunologic, endocrine, metabolic, hormonal, and nutritional factors.<sup>8-11,17</sup> Alterations in immunity following infection, acute inflammation, or incomplete excision have been proposed as mediating factors. Postoperative infection did not occur in our patient, however, alterations in immunity secondary to inflammation following a pneumothorax may have influenced her complete spontaneous regression of biopsy-proven pulmonary metastatic melanoma.

Over the last 5 years, immunological studies of patients with melanoma have revealed that many have cytotoxic T cell (CTL) responses to antigens that are present on melanoma cells. In patients treated with adoptive transfer of tumor-infiltrating lymphocytes, the presence of CTL reactive against gp100-derived epitopes has been correlated with favorable clinical response; these CTL may account for the mechanism of tumor regression in some patients who respond to interleukin-2 (IL-2)-based therapies.<sup>35</sup> Some of these and other defined melanoma antigens are also present on normal cells of melanocytic origin, and patients who respond to IL-2 therapy often develop patchy vitiligo. Our patient did not develop vitiligo. We lacked a source of fresh autologous tumor after our patient went into remission and could not test her for the presence of CTL responses to autologous tumor. We obtained peripheral blood from the patient after her complete remission in hopes that we could determine the presence of CTL responses to defined HLA-A2-associated melanoma peptides such as those derived from MART-1/Melan-A, tyrosinase, and gp100.<sup>36-49</sup> Unfortunately, the patient's HLA type was HLA-A26, B18, B38, and to date, there are no defined epitopes for melanoma-reactive CTL associated with any of these MHC molecules. We plan to look for evidence of CTL responses in this patient as more melanoma epitopes become defined.

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