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PET/CT

Spontaneous regression of a metastatic melanoma pulmonary deposit following biopsy

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ABSTRACT

Spontaneous complete and partial regression of metastatic melanoma is poorly understood, and is a rare phenomenon with less than 80 cases reported since 1866. Several correlations have been noted such as systemic or local infections, operative trauma, hormonal influences, nutrition and immunologic factors. We present FDG PET and CT findings in a patient with multiple pulmonary metastases of melanoma, one of which underwent regression following biopsy. We suggest immune system modulation, triggered by biopsy, could have played a role, although the precise mechanism remains unknown.

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Case report

A 55-year-old woman presented with night sweats, cough, and hemoptysis. Due to a remote history of being homeless, tuberculosis was suspected. Physical examination was unrevealing. Laboratory tests including Complete Blood Count, and a chest x-ray were ordered. While the complete blood count was normal, the chest x-ray showed a well defined round opacity in the left lower lobe (Fig. 1). This was not seen on a previous chest x-ray and was considered unlikely to represent tuberculosis, but highly suspicious for malignancy. Computed Tomography (CT) scan of the chest was performed 10 days later for further characterization. In addition to the left lower lobe pulmonary nodule, smaller cavitory lesions were seen

in the bilateral upper lungs (Fig. 2). A CT-guided biopsy of the left lower lobe nodule was positive for metastatic melanoma. Patient had no history of melanoma and clinical examination did not reveal a primary lesion.

With the diagnosis of melanoma, brain Magnetic Resonance Imaging and F-18 Fluoro Deoxy Glucose (FDG) Positron Emission Tomography (PET)-CT were obtained to assess the extent of metastatic disease. The time interval between the baseline CT and PET-CT was 43 days. On F-18 FDG PET-CT, bilateral upper lobe cavitory lesions had increased in size and number and were markedly hypermetabolic with maximum standardized uptake value (max SUV) of 15.2 (Fig. 3C and D). On the other hand, the previously biopsied left lung nodule has decreased in size and showed very minimal FDG uptake with max SUV of 2.5 (Fig. 3A and B).

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Fig. 1 – Initial chest x-ray showed a well circumscribed left lower lobe nodule. This was new since a previous film 6 years earlier and was concerning for malignancy.

Discussion

Spontaneous regression is, by definition, disappearance of a tumor (complete regression) or decrease in size of a tumor (partial regression) in the absence of treatment. There are case reports of this phenomenon, however, it is considered to be very rare (0.2%). Several correlations have been noted including systemic or local infection, operative trauma, hormonal influences, nutrition, and immunologic factors [1]. Immune system modulation seems to have been a common corresponding factor and has been suggested to play a role [2]. The precise mechanism leading to this phenomenon, however, remains unknown.

Melanoma is thought to result from chronic damage to melanocytes from ultraviolet radiation. Normal immune system will recognize and destroy damaged cells through dendritic cells. These detect tumor-associated antigens and activate cytotoxic T-cells, leading to apoptosis. Helper T-cells support these responses by producing cytokines such as interferon γ , thereby recruiting and activating natural killer cells.

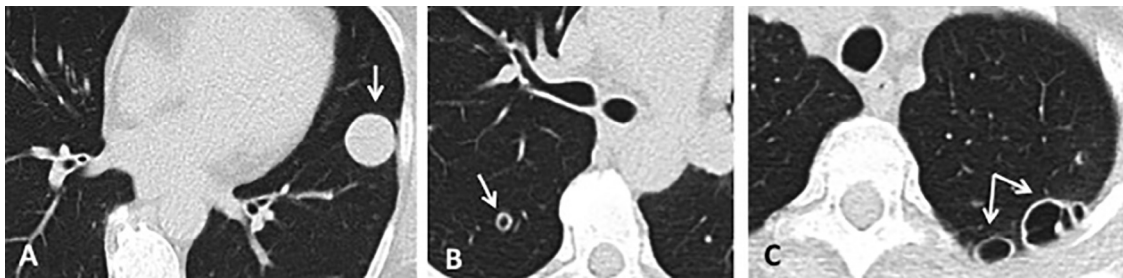


Fig. 2 – Representative images from the initial computed tomography, 10 days later. (A) Axial images in lung window shows a 27×23 mm left lower lobe nodule (arrow). There are additional cavitary lesions in the right upper lobe (B) and left upper lobe (C).

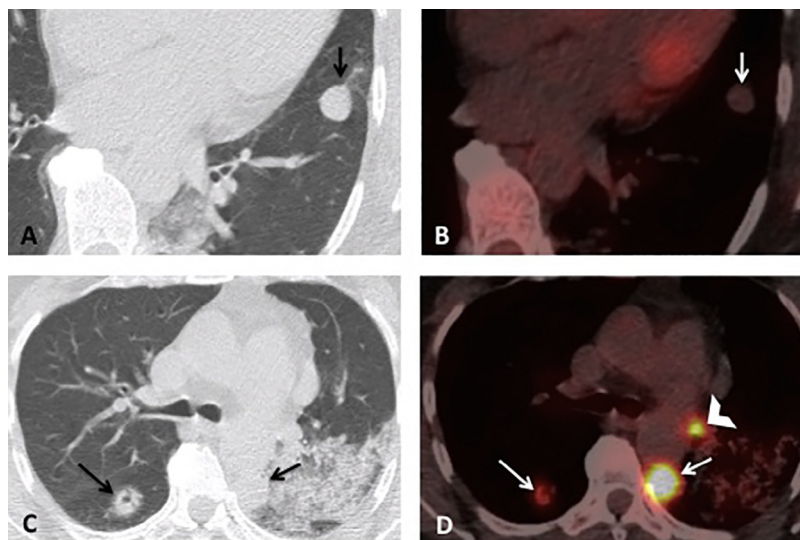


Fig. 3 – Positron emission tomography-computed tomography images, 43 days later. The left lower lobe nodule (A) has decreased to 17×14 mm in size. On the fused image (B) it does not show increased uptake of F-18 fludeoxyglucose. (C) Bilateral upper lobe disease has increased (arrows). These show intensely increased fludeoxyglucose uptake on positron emission tomography (D). Note left hilar nodal spread (arrowhead).

As the tumor evolves, however, it undergoes “immune editing”. Some tumor cells undergo mutations so they no longer express the antigens that are recognized by the immune system. While the immune system continues to kill the cells it recognizes, the latter group, become more dominant in the tumor. Also, some tumor cells actively suppress cytotoxic T-cells by expressing inhibitory molecules such as PDL1, which binds to receptors on the T-cells and deactivates them. This is an example of an “immune checkpoint”.

Additionally, tumor cells can attract immune cells that can inhibit the activity of other immune cells, thereby supporting tumor growth. These inhibitory cells include regulatory T-cells and certain types of myeloid cells. These 2 immune responses are constantly opposing each other at the tumor.

Immunotherapy uses 2 approaches. One aims to strengthen patient’s immune system through vaccines, adoptive T-cell transfer, infusion of stimulating cytokines such as Interleukin-2, and agonist antibodies such as anti-OX40 that will enhance T-cells [3]. The other approach is to target immune checkpoints, for example antibodies that bind to PD1 and stop this molecule from switching off cytotoxic T-cells, or those targeting CTLA4. Blocking this latter molecule helps DCs to drive antitumor T-Cell responses. Not all patients will respond to these immunotherapies and in some, responses will be delayed. Combining immunotherapy with chemotherapy and radiotherapy can lead to a better response in some patients. Immunotherapies can themselves be combined. For example, PDL1 and CTLA4 blockers can improve responses when administered in combination [4].

In cases of spontaneously regressing melanoma, histologic examination has shown infiltration of the tumor by

inflammatory cells [5]. Our patient underwent immune therapy with ipilimumab with a favorable initial response. Unfortunately, as is common with this form of treatment, melanoma recurred with lung, brain, and spinal cord metastases, this time resistant to ipilimumab. Interestingly, despite the recurrence of disease, the biopsied lesion continued to decrease in size throughout the 19 months that followed after initial diagnosis.

We postulate that trauma from biopsy could have induced an inflammatory response and lead to subsequent regression of this lesion although the mechanism leading to this rare phenomenon remains obscure.

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