



## OBJECTIVE

To report a case of metastatic lung adenocarcinoma with uncommonly aggressive course in a patient with multiple sclerosis treated with natalizumab, and to discuss possible mechanisms of the metastatic dissemination.

#### CASE REPORT

A 68 y.o man with active RRMS, based on sustaining a major relapse with severe paraparesis while on INF-beta 1b three years earlier, was switched to natalizumab. The patient remained relapse-free for the duration of the 27 total natalizumab infusions. He presented with new headaches 6 months before diagnosis and death. A brain and cervical MRIs with gadolinium were negative for parenchymal or meningeal process other than MS lesions. Despite symptomatic treatment the headaches worsened and repeat brain MRI showed dural enhancement and unchanged MS lesions. A LP showed normal cell count and PCRs were negative for HVS and VZV. Subsequently the patient developed subdural fluid collections, extensive thoracic vertebral lesions suggestive of metastases and a lung lesion on X-ray suspicious for carcinoma or infection. The patient could not be resuscitated after sustaining cardiac arrest.

Autopsy showed lung adenocarcinoma with diffuse tumor micro-embolization and solid tumor infiltration of heart and regional lymph nodes. A small solitary cerebellar metastasis, diffuse tumor infiltration of the dura not involving the leptomeninges, and a subacute infarct in the right ACA were seen in the brain.





# AGGRESSIVE LUNG ADENOCARCINOMA IN A PATIENT WITH MULTIPLE SCLEROSIS (MS) TREATED WITH NATALIZUMAB

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#### BACKGROUND

There is no clear evidence that there is an increase of cancer in multiple sclerosis8. However there is risk of malignancy with some of the treatments for MS, notably mitoxantrone, and possibly in some newer medications. Lemtrada, as well as some of the older chemotherapy meds such as azathioprine, mycophenolate and others.

In contrast, some DMTs, have started to be tested, strictly on an experimental basis to date. These meds include fingolimod and natalizumab.

Natalizumab, a humanized anti-integrin monoclonal antibody, is an approved treatment for relapsingremitting multiple sclerosis. The mechanism of action is blocking of the VLA-4 receptor on the lymphocyte and other inflammatory cells thereby preventing binding to the VCAM-1 receptor on the surface of the endothelial cell resulting in preventing the transmigration of the lymphocytes beyond the blood-brain barrier into the CNS parenchyma.

To date there have been multiple reports of melanoma, CNS lymphoma and peripheral lymphoma associated with natalizumab treatment in patients with MS3,4,5. This is the first case of lung adenocarcinoma in a patient treated with natalizumab for previous 27 months. This malignancy had a highly aggressive course, in part, due to a less common mode of metastatic dissemination seen in this case, tumor microembolism.

Recent reviews have not shown an increase in melanoma or nevus conversion rate, as well as overall malignancy rates in MS patients on natalizumab. 2,1 However, the guestion of an impact, positive or negative, on the course of the malignancy, after the malignancy has started, on a given patient, including the development and number of metastases, is raised by this case. Consequently, should there be caution for placing MS patients with previously known cancer diagnosis on natalizumab treatment? And, is there an indication for patients that develop solid tumor or hematological malignancy while on natalizumab have this treatment stopped and switched to alternate DMTs?

#### DISCUSSION

The mechanism of action of natalizumab for prevention of clinical relapses and new MRI lesions in MS is blockade of the VLA-4 receptor on lymphocytes and other inflammatory cells resulting in failure of the cells to bind with the VCAM-1 receptor on the endothelial cell surface and therefore prevention of transmigration of lymphocytes into the CNS parenchyma.

In addition to T and B cells, monocytes and myeloid cell lines the VLA-4 receptor is aberrantly expressed in many different neoplastic tissue cell types (lymphoma, myeloma, lung, renal, breast, gastric, prostate, melanoma, ovarian) as well as many available

mammalian and human cell lines. Some neoplasm and certain cell lines express very high levels of V 4 constitutively. Just like normal lymphocytes, car cells can, via the VLA-4/ VCAM-1 interaction and binding, transmigrate through the endothelium into the tissue parenchyma beyond. This may result in formation of metastases.

There is an extensive body of literature showing potent biological effect, both in animal studies and with cell lines, of experimental VLA-4-blocking utilizing monoclonal antibodies or other methods, in modulating cancer biology. In these studies reduction of cancer progression and of metastases is seen with either low expression of VLA-4 on cancer cells or with blocking of the VLA-4 receptors. Similarly increased VCAM-1 expression on endothelial cells has resulted in increase of the metastases. Via other mechanisms VLA-4 also plays a role in neo-angiogenesis promoting survival of tumor cells, in pro-tumor growth fusion of tumor cell with endothelial cell, and mediates

effect for maintenance of chemoresistance of tumor. In many of the experiments both reduction of metastatic disease as well restoration of sensitivity of previously chemotherapy-resistant tumor was demonstrated 5,6.

However, in some circumstances and under certain experimental conditions the opposite effect, i.e. facilitation of metastases, has been shown. This is less common than the therapeutic effect that predominates in most of these in vitro and in vivo studies.

Despite these promising results from animal studies, there has not been, to our knowledge, a proposed human clinical trial for cancer treatment with these antibodies. Also, to our knowledge, none is planned with natalizumab. The unpredictability of the biological effect in humans vs animals, the uncertainty about the dominant mechanism of VLA-4 blockade function, the possible suppression of tissue immunesurveillance for cancer development are some of the issues to be addressed before any such clinical trial.

In this case of very aggressive lung adenocarcinoma it is unclear if VLA-4 binding with the 27 month-long duration of natalizumab treatment had any effect on the course of the disease, positive or negative. We postulate that the rapid growth of the lung tumor and rapid rate and extend of metastases development is related to this mechanism of tumor microembolization seen at autopsy. We have not studied autopsy tissues for either VLA-4 or VCAM1 expression.





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### CONCLUSIONS

- 1. This is the first case to be reported, outside the natalizumab postmarketing study1, of metastatic lung adenocarcinoma with aggressive course on a natalizumab-treated multiple sclerosis patient.
- 2. Although there is no current evidence that increased rate of malignancy is associated with natalizumab treatment, this case raises questions of the impact of treatment with this medication on the course of the disease on a given patient, including aggressive vs more indolent growth, and on number of metastases.
- 3. Theoretically, and by preponderance of experimental evidence2,3,4,5, blockade of the VLA-4 receptor, by natalizumab or other method, may have a beneficial effect in the rate of development and number of metastases. However, under certain experimental or clinical conditions the opposite effect may be observed. In this reported case it is unclear if there was worsening, benefit or no net effect in the course of this rapidly evolving lung adenocarcinoma in this case.
- 4. Future experimental studies and clinical trials may provide additional insights of mechanisms of natalizumab effect, if any, on cancer biology and if there is a potential therapeutic effect to be exploited.

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