



## Shrinkage of Melanoma Metastases Following High Dose Intravenous Immunoglobulin Treatment

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Despite primary resection of tumors, the hazard of recurrences in most patients prevents cure from the disease. Therefore, continuous efforts are made to overcome "resistant" metastases as well as metastases residing in "sanctured" locations.

Intravenous immunoglobulin is a preparation of normal polyspecific immunoglobulin G obtained from pooled plasma of a large number of healthy donors. In recent years IVIG has increasingly been used in the treatment of patients with a variety of autoimmune and systemic inflammatory diseases, including Kawasaki syndrome, dermatomyositis, systemic lupus erythematosus, antiphospholipid syndrome, and juvenile rheumatoid arthritis [1]. The effect of IVIG is mediated through several mechanisms, including inhibition of complement-mediated damage, changes in the inflammatory potential of circulating immune complexes, modulation of the relative production of pro-inflammatory and anti-inflammatory cytokines, modulation of expression of adhesion molecules and chemokines, and neutralization of microbial toxins [1].

There is a bi-directional relationship between autoimmunity and cancer. Malignant conditions are frequently associated with autoimmune phenomena. Examples include: an increased inci-

dence of Eaton-Lambert myasthenia-like syndrome in patients with small cell carcinoma of the lung, thymoma in patients with myasthenia gravis, different types of epithelial malignancies or lymphoproliferative malignancies in patients with autoimmune hemolytic anemia, thrombocytopenia or neutropenia, and melanoma associated with vitiligo [2]. Conversely, there is an increased risk of cancer in autoimmune conditions as exemplified by the emergence of ovarian carcinoma in patients with dermatopolymyositis [2], lymphoproliferative diseases in patients with rheumatoid arthritis, SLE and Sjogren's syndrome, lung cancer in scleroderma patients, and thyroid papillary carcinoma in patients with autoimmune thyroid diseases. The cancer may appear at the time of diagnosis of the autoimmune disease or several years later [2].

A reduction in the number of lymphocytes was demonstrated in patients with chronic lymphocytic leukemia who were treated with IVIG to prevent infections. This effect was attributed to the anti-leukemic effect of IVIG [3]. Also, regression of Kaposi's sarcoma was noted in a human immunodeficiency virus patient treated with IVIG [4].

Our previous experimental experience using IVIG to prevent metastatic spread [5] in a patient with widespread mela-

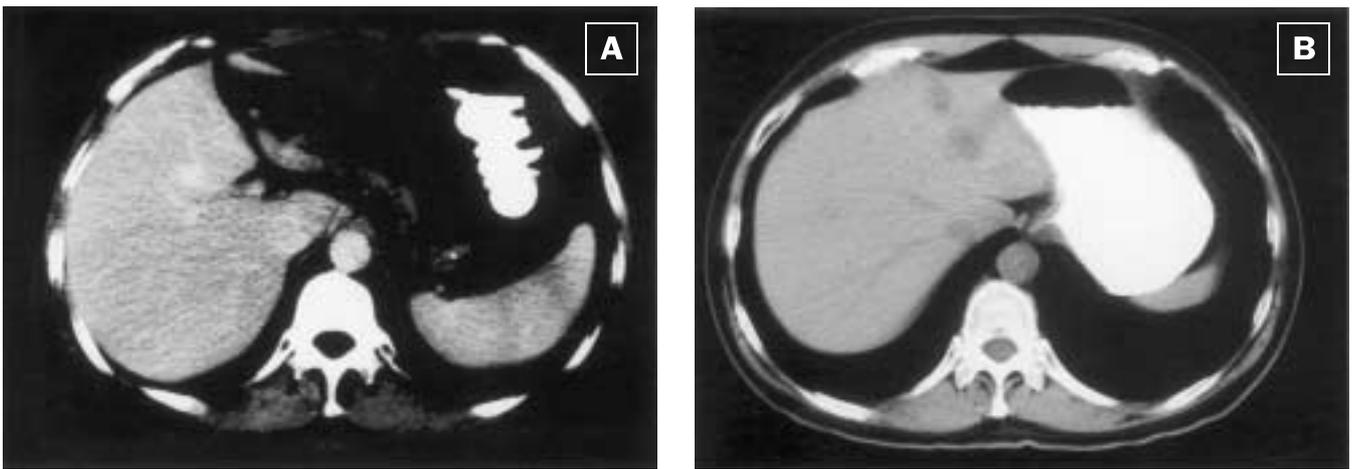
noma supports the above findings. Although just a single case, it aptly demonstrates how implementation of this harmless therapy, already used in many autoimmune patients, is beneficial in patients afflicted with tumors.

### Patient Description

A 39 year old man was referred to the dermatology unit at Sheba Medical Center because of a change in color from black to green of his left hip nevus during the previous 3 months. A wide excision of the nevus was performed and the pathologic examination disclosed superficial spreading melanoma. A work-up did not disclose metastases. After 18 months follow-up, a solitary lymph node emerged in the left groin. Computerized tomography confirmed the large lymph node in the groin without additional metastases. Radical lymph node dissection of the femoral and iliac area was performed with hyperthermic perfusion therapy. About 6 months later, a CT scan of the chest, abdomen and pelvis disclosed five small nodules (the largest being 1 cm in diameter) in the lung and about six new lesions in the liver (the largest 4 x 3.5 cm) [Figure A]. At this stage the patient refused chemotherapy. He was offered high dose (2 g/kg) monthly IVIG therapy (Isiven, Lucca, Italy), which was initiated in March 1993. A repeated CT one month later did not demonstrate enlargement of the

IVIG = intravenous immunoglobulin

SLE = systemic lupus erythematosus



CT scan of liver performed before [A] IVIG treatment, indicating large liver metastases, and [B] after three courses of IVIG (2 g/kg body weight). No metastases were detected.

metastases. Six months after the initiation of the IVIG therapy the size of the five lung metastases was without significant change (all of them less than 1 cm) with two additional small nodules (< 0.5 cm). The liver metastases regressed significantly (the largest to 1.5 x 1 cm) without appearance of new hepatic lesions. Two months later the lung metastases were without significant change, and the liver metastases continued to shrink in size [Figure B]. There were no side effects from the IVIG treatment and the patient functioned well.

After about 9 months from the initiation of the IVIG therapy new subcutaneous and bony metastases appeared. During the next 6 months those metastases continued to grow, although there was no significant change in the lung and hepatic metastases. The patient was treated with combination chemotherapy of interferon and IVIG, without regression of his bone and subcutaneous metastases. He died in a septic condition 14 months after the start of IVIG.

## Comment

This is the first report pointing to the probable efficiency of high dose IVIG in cases of unresponsive widespread metastases of melanoma. The implementation of this treatment in our patient led to stability and non-progression of the metastases in several organs, while

leading to regression of metastases in other organs without additional intervening therapies. In all, this therapy resulted in the prolonged survival time of this patient. Although just a single case report, and dealing with melanoma that may occasionally regress spontaneously due to other causes, the remarkable outcome supports previous experimental studies as well as reported clinical experience [3,4].

Previously [5], we reported our results on thousands of mice transplanted with diverse histological tumors and treated by both high (i.v.) and low (subcutaneous) IVIG. The administration of IVIG to mice inoculated i.v. with melanoma or sarcoma cells induced a statistically significant inhibition of metastatic lung foci and prolongation of survival time. Similar results were seen with SCID mice inoculated with SK-28 human melanoma cells. In a different model, melanoma was induced in the footpad, followed by leg amputation after the development of the tumor lesion. A lower number of melanoma recurrences and prolongation of survival time were demonstrated in the IVIG-treated groups.

The IVIG most probably leads to tumor and metastases regression in multi-mechanistic ways, as summarized by us [5]. Nonetheless, IVIG affects each step of the process of metastatic spread – from angiogenesis to direct killing of the malignant cell apoptosis. IVIG may

stimulate both interleukin 12 secretion and natural killing cell activity. IVIG may bind directly to tumor and metastatic cells, leading to complement-dependent and independent toxicity.

In conclusion, the present report points to the implementation of IVIG in some patients with cancer metastases. IVIG is a relatively safe product with few side effects.

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