Neuropsychiatric Complications Associated with Interferon - Alpha -2b treatment of Malignant Melanoma

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Abstract
Several adverse effects have been associated with interferon alpha 2b treatment and neuropsychiatric effects have also been commonly reported. Psychosis and mood disorders have been described in the literature. This case report is of a 30 year old man with malignant melanoma stage 3a who was receiving adjuvant alpha 2b interferon and developed a manic episode two weeks post switching after one month of treatment on a high dose to a low dose. There was no previous psychiatric illness and no known family history of mental illness. This is in keeping with previous reports that mania has been observed in patients undergoing interferon treatment especially after significant dose-reduction or treatment breaks. Mania induced by interferon responds well to antimanic drugs .Since interferon alpha 2b is now commonly used in the treatment of malignant melanoma and other conditions, the need to be aware of its neuropsychiatric complications is essential.

Key words: Melanoma; Treatment; Mania

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Introduction

Interferon preparations such as interferon alpha are widely used in the treatment of a number of non malignant and malignant conditions including malignant melanoma where it used. Mania has been observed in patients undergoing interferon treatment especially after significant dose-reduction or treatment breaks.[1] Malignant melanoma accounts for about 3% of all cancers.[2]

Treatment for early stage malignant melanoma includes local excision, lymph node dissection. Adjuvant therapy with immunmodulatory agent has been used for patients with high risk early stage.[1] As with most systemic treatment, it has some side effects which can be divided into constitutional, hematological , hepatic and neuropsychiatric effects.[1,4]

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Case history

A 30 year old single male was diagnosed with malignant melanoma following discovery of a perineal mole. This was excised and found to be a nevoid spitzoid melanoma.(Clarke's level 5, Breslow thickness 11mm). Wide local excision did not show residual cancer. Sentinel node biopsy of his left groin was positive for melanoma. He subsequently underwent a block dissection of his left groin and 14 nodes were all negative. CT scan of his chest, abdomen and pelvis were negative for metastastic disease. Following discussion regarding risk and benefit he was commenced on adjuvant Interferon alpha. The planned schedule administration was 20 million iu/m^2 intravenously day 1 to5 for 4 weeks and then 10millioniu/m^2 subcutaneously on day 1,3 and 5 for subsequent 48 weeks. He tolerated the first part well. During week three of the maintenance dose he became physically aggressive at home, assaulted a taxi driver and was brought to hospital. Collateral history from his relative suggested a gradual change in his behaviour about a week prior to presentation to hospital as he was becoming more irritable,

hyperactive, not sleeping at night and was expressing grandiose thoughts.

Mental state examination revealed a markedly restless man with distractibility and increased psychomotor activity. He was talking excessively with flight of ideas. His mood was elated and his thought content revealed grandiose delusions.

There was no evidence of perceptual disturbance. He was well oriented with intact memory but no insight. A provisional diagnosis of mania with psychotic symptoms was made.[3] As it was his first episode of mania with no previous psychiatric history, no known family history of mental illness, no history suggestive of current or past illicit drug use, a full physical investigation was done. This consisted of blood work up and MRI brain scan. There were no significant findings. His alpha Interferon was stopped and he was commenced on Olanzapine while in hospital. He responded to Olanzapine and by the third week of treatment his mood was euthymic. Due to the temporal association between the onset of his first manic episode and Interferon treatment the final diagnosis was an organic mood disorder.[3] He was closely monitored by our psychiatric out patient department in collaboration with the oncology department. However within a month he was readmitted to hospital with a manic relapse precipitated by non compliance with medication. His presentation was similar to his first episode but with more florid psychotic features consisting more of persecutory delusions. His symptoms resolved after about a month of recommencing treatment with Olanzapine and was discharged with some plans in place to ensure compliance.

Discussion

According to the WHO the incidence of melanoma cases worldwide is increasing faster than any other cancer.[5] Recent evidence suggests that melanoma incidence may have reached a peak. The annual increase in incidence rate varies between populations but in general has been in the order of 3-7% per year for fair skinned Caucasians.[6,7]

Treatment of primary melanoma consists of surgical excision and treatment for regional metastasis includes additional surgery, lymph node dissection. Other additional therapies include radiation, chemotherapy and administration of chemoimmunotherapy.

In 1996, Kirkwood et al published the results of ECOG1684 (Eastern Coopearative Oncology Group) which demonstrated both a disease free and overall survival benefit for patients with stage 3 (lymph node positive) melanoma treated with high dose of IFN alpha.[8] Other studies have not demonstrated overall survival advantage. Concerns however have been raised regarding the toxicity of Interferon therapy. These effects can be grouped into two main categories: constitutional reactions and neuropsychiatric complications. The constitutional reactions that have been described include fever, malaise, flu like symptoms which occurs after treatment initiation and later reactions following sustained treatment. Neuropsychiatric complications include acute confusional state, depressive episode which develops more slowly over weeks to months of treatment and symptoms of mania and hypomania.[8,9] Depression is widely recognized as an adverse effect in relation to Interferon therapy and up to10% of patients may become overtly depressed. However, unlike depression the development of manic symptoms in a patient receiving Interferon is at times un-recognised especially if the symptoms are not classical. There is increasing evidence that the development of manic symptoms can occur as a result of treatment with Interferon. There have been case reports of mania occurring mostly within the context of abrupt withdrawal of Interferon therapy or especially after patients undergo significant dose reduction.[1] The current case report describes a case of a first episode of mania following planned dose reduction in a patient undergoing therapy with Interferon for malignant melanoma. This suggests a temporal association between the reduction of Interferon alpha and onset of the manic episode especially in the absence of a past psychiatric history. This further supports the increasing evidence that treatment with Interferon is closely linked to the development of mania or hypomania according to the ICD-10 criteria for their diagnosis.

Conclusion

This case report further supports the view that the development of manic symptoms is associated with a significant dose reduction or abrupt withdrawal from Interferon as well as also highlighting the importance of considering psychiatric evaluation as part of the screening process for patients being considered for Interferon therapy- and not only those with high risk of mental illness. Patients on Interferon therapy should be regularly assessed for psychiatric symptoms while on treatment, specifically when contemplating dose changes.

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