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Meningeal Fluid Granulocytosis After Cytarabine

M. Flasshove, H.J. Schütte, R. Kellner, K. Höffken and S. Seeber

WE REPORT recurrent meningeal fluid granulocytosis after intermediate-dose intravenous cytarabine. The indication for therapy was first relapse of acute lymphoblastic leukaemia (ALL) in a 33-year old man.

14 years ago the patient had undergone subtotal nodal irradiation and splenectomy for Hodgkin's disease. After 12 years without disease he developed ALL and was treated with combination chemotherapy and prophylactic central nervous system (CNS) irradiation with 24 Gy [1], with some modifications including cytarabine and mitoxantrone as consolidation therapy and prophylactic treatment for CNS relapse with intrathecal application of cytarabine, methotrexate and dexamethasone (AMD). He achieved complete remission and stayed on maintenance therapy with mercaptopurine, methotrexate and bimonthly intrathecal AMD for 8 months before he was admitted with clinical signs of acute meningitis. Microbiological examination of the cerebrospinal fluid (CSF) revealed pneumococcal bacteria and the patient recovered after antibiotics.

2 months later bone-marrow biopsy showed relapse of ALL and the patient was put on a 3 h intravenous infusion of cytarabine 1 g/m^2 every 12 h for 8 doses with aclacinomycin 20 mg/m^2 on days 2–6. Prophylactic oral ofloxacin was started on the first day. After 5 doses of cytarabine, chemotherapy was halted because the patient developed a sterile meningitis. CSF analysis revealed a pleocytosis of 6600/3 granulocytic cells, increased protein levels in the absence of lymphoblasts or viral, bacterial or fungal microorganisms. Nevertheless, broad specific antibiotics were administered. Nuclear magnetic resonance scans of the brain did not show any abnormalities. The symptoms and the pleocytosis disappeared within 4 days.

Because of persisting blasts in the bone marrow a second course of chemotherapy was started 4 weeks later. Again, on the second day of the treatment, the patient showed the clinical signs of a meningitis with a granulocytic pleocytosis (1200/3 cells) without evidence of any microbiological agents in the CSF. This time chemotherapy was continued with concomitant antibiotics. Symptoms improved within a few days. Because of a residual blastic infiltration of the bone marrow, a third chemotherapy course was administered 4 weeks later. After 3 doses, meningeal symptoms occurred and the patient again soon recovered despite continuing chemotherapy.

The neurotoxicity of high-dose cytarabine regimens has been frequently reported. It appears to be age-related [2] and to occur in a dose-dependent manner, increasing rapidly beyond a total dose of 48 g/m^2 per course [3]. The major sign is the cerebellar syndrome with some other features such as seizures, leukoencephalopathy and peripheral neuropathy occurring significantly less often [4]. Pre-existing CNS disorders as well as the cumulative amount of cytarabine received may play a role in the development of neurological symptoms [4, 5].

Our patient developed a sterile meningitis with classical clinical symptoms and granulocytic pleocytosis shortly after the onset of three courses of cytarabine. Several CSF analyses were performed without detection of any microorganisms. Each time the patient recovered quickly, as opposed to the prolonged recovery time observed for bacterial meningitis. No other neurological toxicity was observed. To our knowledge, meningitis or meningitis-like syndromes have not been previously described after cytarabine. The fact that severe and reproducible neurotoxicity occurred in our case with only intermediate-dose cytarabine may be explained by the pre-existing CNS disorder (pneumococcal meningitis 2 months ago) and the previously received cytarabine as part of induction and consolidation.

1. Hölzer D, Thiel E, Löffler H, *et al.* Intensified therapy in acute lymphoblastic and acute undifferentiated leukemia in adults. *Blood* 1984, **64**, 38–47.
2. Gottlieb D, Bradstock K, Koutts J, Robertson T, Lee C, Castaldi P. The neurotoxicity of high-dose cytosine arabinoside is age-related. *Cancer* 1987, **60**, 1439–1441.
3. Herzig RH, Herzig GP, Wolff SN, Hines JD, Fay JW, Phillips GL. Central nervous system effects of high-dose cytosine arabinoside. *Semin Oncol* 1987, **14** (Suppl. 1), 21–24.
4. Baker WJ, Royer GL Jr, Weiss RB. Cytarabine and neurologic toxicity. *J Clin Oncol* 1991, **9**, 679–693.
5. Nand S, Messmore HL Jr, Patel R, Gross Fisher S, Fisher RI. Neurotoxicity associated with systemic high-dose cytosine arabinoside. *J Clin Oncol* 1986, **4**, 571–575.

Correspondence to M. Flasshove.
The authors are at Department of Internal Medicine (Cancer Research) West German Tumor Center, University of Essen Medical School, Hufelandstr. 55, 4300 Essen, Germany.
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Mitozantrone-induced Onycholysis

Paul L.R. Mitchell and Vernon J. Harvey

MITOZANTRONE IS an anthracene derivative with substantial cytotoxic activity in breast cancer, lymphoma and some leukaemias. Only 2 cases of onycholysis have been described with mitozantrone as a single agent [1] and a further 4 cases in

Correspondence to P. Mitchell.
The authors are at the Department of Clinical Oncology, Auckland Hospital, Park Rd, Auckland, New Zealand.
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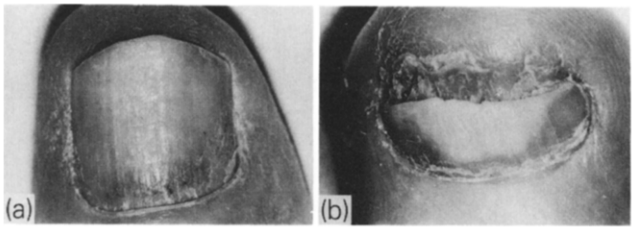

Fig. 1. Onycholysis affecting fingernails (left) and toenails (right) during mitozantrone therapy of advanced breast cancer.

combination with doxorubicin [2]. We report 2 cases seen in 297 patients (279 breast cancer, 18 ovarian cancer) treated with single-agent mitozantrone.

Case 1

A 59-year-old man with extensive local recurrence of adenocarcinoma of the breast had previously been treated with tamoxifen, megestrol acetate and aminoglutethimide as well as local radiotherapy to the supraclavicular area. Mitozantrone was started at a dose of 32 mg (14 mg/m^2) and was well tolerated without alopecia. After four cycles he developed nail tenderness and nail bed erythema, rapidly leading to thickening and lifting of the thumbnails and all toenails (Fig. 1). Fungal culture was negative but a superimposed bacterial infection improved with oral amoxycillin/clavulanic acid. The nail changes persisted during a further three cycles of mitozantrone, slowly returning to normal only after treatment was changed to cyclophosphamide, methotrexate, 5-fluorouracil and prednisone (because of progressive disease).

Case 2

A woman aged 59 with ovarian carcinoma; six cycles of carboplatin led to partial response following surgery, but relapse 5 months later. Mitozantrone was started at an initial dose of 21 mg (12 mg/m^2) with moderate nausea and vomiting but no alopecia. Other regular medications were spironolactone, diclofenac, triazolam and metoclopramide. Thickening, tenderness and lifting developed in several fingernails after three cycles while similar changes developed in the nails of both great toes during the fourth and final cycle. There was improvement of nailbed haemorrhage and exudate in the fingernails with topical clotrimazole cream and oral amoxycillin/clavulinic acid, but the nails only returned to normal 3 months after treatment was changed from mitozantrone to megestrol acetate.

Both patients developed onycholysis affecting multiple nails shortly after starting mitozantrone and then slowly improved on its cessation, strongly suggesting this to be the aetiological agent. A similar pattern has been described in 2 other cases receiving single agent mitozantrone [1]. Onycholysis as an isolated dermatological toxicity of chemotherapeutic agents is uncommon, and appears to be confined to anthracyclines [3] and their synthetic derivatives.

1. Speechley-Dick ME, Owen ERTC. Mitozantrone-induced onycholysis. *Lancet* 1988, **2**, 113.
2. Van Belle SJP, Dehou M-F, De Bok V, Volckaert A. Nail toxicity due to the combination Adriamycin–mitozantrone. *Cancer Chemother Pharmacol* 1989, **24**, 69–70.
3. Cunningham D, Gilchrist NL, Forrest GJ, Soukop M. Onycholysis associated with cytotoxic drugs. *Br Med J* 1985, **290**, 675–676.

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Malignant Melanoma: Treatment of Metastatic Meningitis with Intrathecal Interferon alpha-2b

T. Dorval, P. Beuzeboc, E. Garcia-Giralt, M. Jouve, T. Palangie and P. Pouillart

THE MENINGES are frequently involved during the dissemination of malignant melanoma. The most frequent primary tumours in meningeal carcinomas are breast and lung cancer; malignant melanoma ranks third or fourth with a relative risk higher than that of any other solid tumour [1]. Meningeal carcinomatosis in malignant melanoma is always associated with a rapidly fatal course of the disease. Conventional approaches to this complication do not affect the prognosis. The use of intrathecal chemotherapy with methotrexate and/or cytarabine is ineffective and systemic chemotherapy provides very poor results [2].

Interferons have demonstrated a therapeutic role in treating disseminated malignant melanoma with a reported response rate of about 20% in phase II trials [3] and can be safely administered intrathecally [4]. Moreover, as interferons have shown anticancer activity in meningeal leukaemia [5], we treated a young patient with intrathecal interferon.

The patient, 23 years old, presented with metastatic malignant melanoma confined to skin and lymph nodes and received recombinant DNA interferon (IFNα_{2b}) at a dose of 10^6 international units (U) subcutaneously three times a week. After 1 month of treatment during which there was no change in tumour size the patient complained of headache, nausea, vomiting and photophobia. A lumbar puncture was performed and cerebrospinal fluid (CSF) analysis confirmed metastatic meningitis with presence of tumour cells, raised CSF albumin and decreased CSF glucose. A computed tomography scan of the brain did not show evidence of brain metastasis. The patient received an intrathecal injection of interferon three times a week at an increasing dose from 3–10 $\times$ 10^6 U per injection, according to clinical and laboratory tolerance. Systemic administration of interferon was stopped. Assessment consisted of clinical examination, blood count, blood chemistry and CSF analysis. Functional symptoms slowly abated and disappeared within 2 weeks of therapy; CSF examination showed a dramatic decrease in tumour cell count and cytological and chemical normalisation after the eighth injection. General safety of therapy was excellent as no side effects were observed.

When CSF normalisation was acquired and because of a persistent extrameningeal metastatic disease, interferon was administered both intrathecally once a week and subcutaneously three times a week. The side effects were moderate and did not require any modification of therapy; meningeal cytological remission was checked weekly and persisted. The patient died 3 months later from malignant pericarditis. Interferon warrants further study as a treatment for meningeal carcinomatosis in melanoma.

Correspondence to T. Dorval.
The authors are at the Service de Medecine Oncologique, Institut Curie, 26 rue d'Ulm, 75231 Paris, France.
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