Anti-Cancer Drugs 2002, **13,** pp. 327–330

Case report

Life-threatening anaphylactoid reaction to amifostine used with concurrent chemoradiotherapy for nasopharyngeal cancer in a patient with dermatomyositis: a case report with literature review

Janette Vardy,[1,2] Edmond Wong,[2] Michael Izard,[3] Anthony Clifford[1,2] and Stephen J Clarke[1,2]
[1]Royal Prince Alfred Hospital, Sydney, NSW 2050 Australia. [2]Concord Repatriation & General Hospital, Sydney, NSW 2139, Australia. [3]Department of Radiotherapy, Mater Misericordiae Hospital, North Sydney, NSW 2060, Australia.

Dermatomyositis is associated with malignancy in approximately 20–25% of cases. The most common associated cancers are ovarian, lung, pancreatic, stomach, colon and non-Hodgkin's lymphoma. Nasopharyngeal cancer is not common in the Caucasian population; however, there is a much higher incidence in Asian patients. Radiotherapy is the mainstay of treatment for early nasopharyngeal cancer, but combination chemoradiotherapy is becoming more common for patients with advanced disease since the Intergroup trial 0099 demonstrated improved progression-free survival and overall survival for chemoradiotherapy. Increasingly, the cytotoxic agent amifostine is being used prior to radiotherapy in an attempt to decrease associated morbidities. Amifostine has been found to significantly decrease acute and chronic xerostomia but not mucositis. It appears to be selectively protective to salivary glands and kidneys without being tumor protective. The most common side effects associated with amifostine are nausea, vomiting, hypotension, hypocalcemia and allergic reactions. We describe the case of a man with dermatomyositis and stage IV nasopharyngeal cancer treated with chemoradiotherapy and s.c. amifostine. The patient suffered a life-threatening anaphylactoid reaction to amifostine. [© 2002 Lippincott Williams & Wilkins.]

Key words: Amifostine, anaphylactoid reaction, chemoradiotherapy, cytoprotective agent, dermatomyositis, nasopharyngeal carcinoma.

Case review

A 51-year-old man of Malaysian–Chinese origin developed a red, scaly rash over his face and neck. The rash was mildly itchy and photosensitive. An initial diagnosis of eczema was made and he was commenced on steroid cream. Three months later he developed mild shoulder and hip weakness with fatigability. There was no myalgia or tenderness. The muscle weakness progressed over the following 2 months. He then noticed difficulty swallowing dry and sticky foods. There was no dysarthria.

A clinical diagnosis of dermatomyositis was made and the patient admitted to hospital for further investigations. He reported a 4-kg weight loss over a 3-month period. He also complained of chronic nasal congestion, 'fullness in the ears' and mild epistaxis. He denied any change in bowel habits, dyspnea, cough, hemoptysis or fevers.

On examination he was a well-looking man with an obvious photosensitive rash on his face, neck and the dorsum of the fingers. Neck examination revealed bilateral cervical lymphadenopathy with two 2-cm lymph nodes in the left posterior triangle and one on the right, which were hard but not fixed. Oral examination was normal but bilateral middle ear effusions were present on otoscopy. Cranial nerve examination was normal, with no ptosis or fatigability of the extraocular muscles. Neurological examination of the limbs showed mild weakness of the shoulder abductors and hip flexors. Reflexes, coordination and sensation were normal. The patient exhibited nasal speech but his voice was not hoarse or soft.

Cardiovascular, respiratory, abdominal and joint examination were all normal.

Investigations revealed a normal full blood count and biochemistry with the exception of an elevated creatinine kinase (328 IU) and lactate dehydrogenase

Correspondence to J Vardy, Sydney Cancer Centre, Level 6, Gloucester House, Missenden Road, Camperdown, NSW 2050, Australia.
Tel: (+61) 2 9515 6111; Fax: (+61) 2 95159 1546;
E-mail: jvardy@canc.rpa.cs.nsw.gov.au

(268 U/l). Erythrocyte sediment rate was normal. Anti-nuclear antibodies showed a speckled pattern with a titer of 1:160. All other immunological investigations were negative.

Skin biopsy of the rash revealed a lichen reaction with negative immunoflourescence consistent with dermatomyositis (Figure 1). A fine needle biopsy of the cervical lymph node showed malignant large cells. Nasoendoscopy revealed a soft tissue mass in the nasopharynx. Biopsy demonstrated a poorly differentiated large cell carcinoma (Figure 2).

A computed tomography (CT) scan and subsequent magnetic resonance imaging showed a large soft tissue mass filling the nasopharynx, eroding the clivus, and extending superiorly into the sphenoid sinus and right middle cranial fossa (Figure 3). Multiple enlarged lymph nodes were seen in the deep cervical chain. CT scans of the chest, abdomen and pelvis were normal.

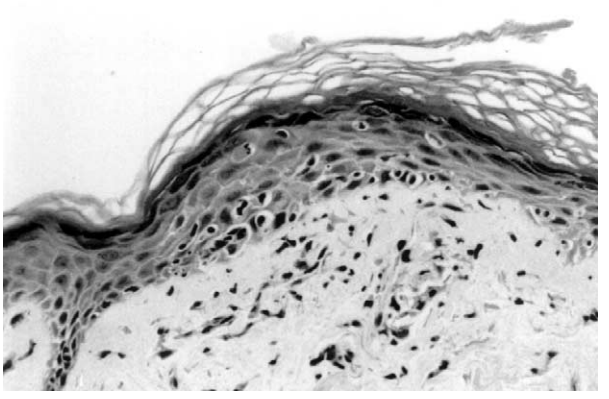

Figure 1. Skin biopsy: lichenoid tissue reaction with basal cell vacuolar change, occasional apoptotic cells and exocytosis of lymphocytes.

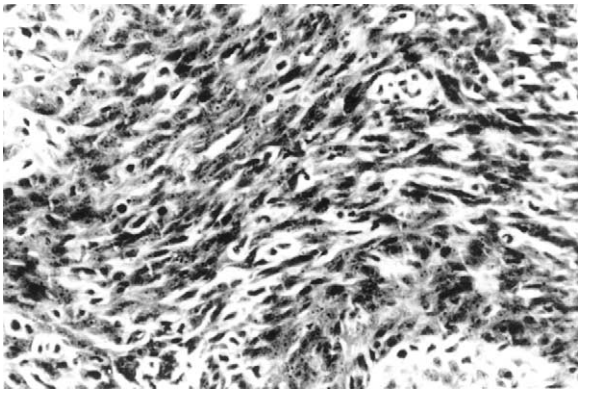

Figure 2. Nasopharyngeal carcinoma comprising sheets of large poorly differentiated epithelial cells (keratin positive) with numerous infiltrating lymphocytes.

A diagnosis of nasopharyngeal carcinoma was made and the patient was commenced on prednisone for his dermatomyositis with mild improvement in his myopathy and rash. It was decided to treat the malignancy with concurrent chemoradiotherapy. A percutaneous endoscopic gastrostomy was inserted prior to radiotherapy. It was planned to give him cisplatin (100 mg) and 5-fluorouracil (5000 mg over 5 days) in weeks 1, 6, 13 and 17 with radiotherapy over 7 weeks commencing in week 1. The patient's Radiation Oncologist recommended the use of the cytoprotective agent amifostine. The amifostine was given s.c. 30 min prior to radiotherapy (200 mg/m^2/day; 325 mg daily).

Following the eighth fraction of radiotherapy the patient was admitted with rigors and a temperature of 40°C. Blood pressure was 80/60. He did not appear to be systemically unwell and on examination there was no obvious source of sepsis with the exception of oral mucositis. The white cell count was 5.5×10^9/l with neutrophils of 5.3×10^9/l. A chest X-ray (CXR) and urine analysis was normal. Blood and urine were cultured, and he was commenced on i.v. ticarcillin sodium and potassium clavulonate, gentamicin and metronidazole.

After radiotherapy the following day the patient noticed an erythematous rash on the trunk and thighs suggestive of a drug reaction rash. The ticarcillin was thought to be the most likely cause, and as he was not systemically unwell the ticarcillin was ceased and oral clindamycin commenced. During a 2-day break from radiotherapy over a weekend the rash improved, the blood pressure stabilized and he defeveresced. He attended radiotherapy on the Monday and later that day was noted to be hypotensive with a blood pressure of 60/40 and a temperature of 39°C. The rash had reappeared with increased severity. A septic work-up was repeated; however, there was still no obvious source of sepsis, and he was commenced on cefotaxime and gentamicin. The blood pressure did not improve with i.v. normal saline or colloid. Intravenous hydrocortisone and phenergan were administered as well as intramuscular adrenaline. There was only a temporary improvement in blood pressure with the adrenaline. He began to develop neck and facial swallowing, and his condition quickly deteriorated although his Glasgow Coma Scale remained at 15/15. There was no bronchospasm; however, the patient became increasingly short of breath and developed bibasal crackles consistent with fluid overload.

The patient was transferred to the Intensive Care Unit where an adrenaline infusion was required for 2 days to maintain his blood pressure. Gas exchange

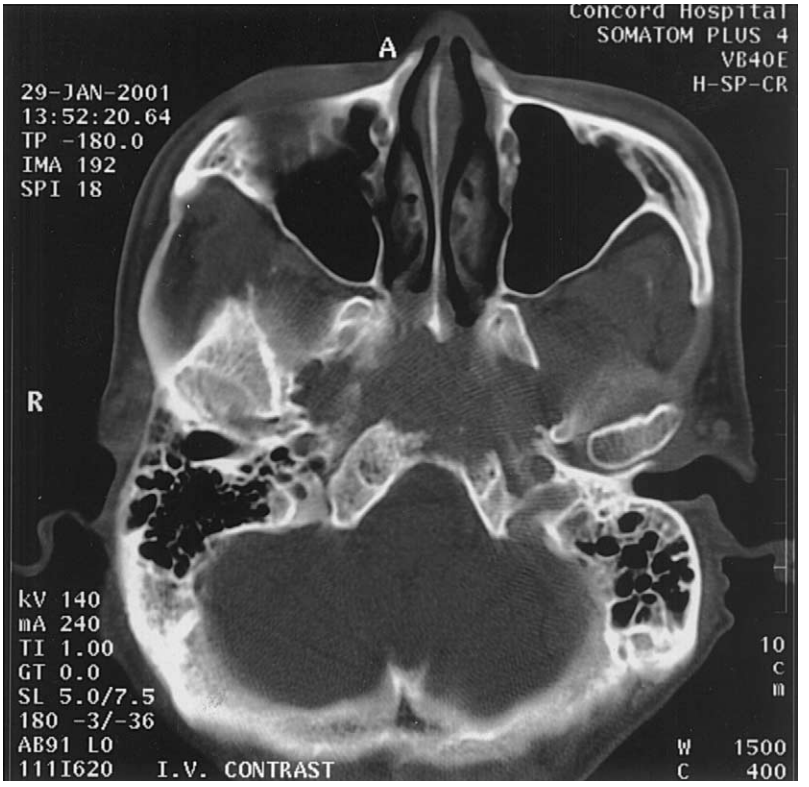

Figure 3. Nasopharyngeal mass extending superiorly into the sphenoid sinus and right middle cranial fossa with erosion of the clivus.

remained stable and intubation was not required. Intravenous antibiotics were broadened with meropenem and gentamicin. An initial CXR was consistent with volume overload and subsequent CXRs revealed mild right lower lobe collapse. The rash improved over the next 4 days. There was never any evidence of sepsis with a normal full blood count and an extensive septic work-up was negative.

The most likely explanation is an anaphylactoid reaction to the amifostine. The temperatures commenced after eight doses of amifostine and after the ninth dose the rash developed. All symptoms improved with a 2-day break in treatment. Rechallenge on the Monday resulted in a life-threatening anaphylactoid reaction.

After 1 week the patient was able to resume radiotherapy without amifostine.

Discussion

Radiotherapy is the mainstay of treatment for nasopharyngeal cancer; however, the use of concurrent chemotherapy has been found to improve survival.[1] The main toxicities associated with radiotherapy for head and neck cancer are acute and chronic xerostomia and acute mucositis.

Amifostine is an organic thiophosphate. It is a prodrug, which is metabolized to WR-1065 the active agent. The drug accumulates in the salivary glands and kidneys. It was initially found in animal studies to be protective of normal tissue, particularly the salivary glands and kidneys, without being tumor protective to treatment with radiotherapy and some chemotherapeutic agents, especially cisplatin. Its mode of action is thought to be scavenging of radiation-induced free radicals, which protect the cellular membrane and DNA from damage.[2–5] Its selectivity is likely to result from the increased alkaline phosphatase activity which dephosphorylates the amifostine to the free thiol, higher pH and better vascularity in normal tissues compared to tumors.[5]

A phase III trial by Brizel *et al*. randomized 303 head and neck cancer patients to radiotherapy with or without 200 mg/m^2 i.v. amifostine administered 15–30 min prior to treatment. They concluded that patients treated with amifostine had significantly less acute and chronic xerostomia, increased median saliva production, but no decrease in mucositis.

Importantly, there was no significant difference in two-year local-regional control (58 versus 63%), disease-free survival (53 versus 57%) or overall survival (71 versus 66%). The amifostine was reportedly well tolerated; however, 21% of patients ceased it prior to completion of their radiotherapy. The most common side effects were nausea and vomiting, transient hypotension, and allergic reactions. None of the allergic reactions were serious enough to result in hospitalization. Nausea and/or vomiting occurred in 53% of patients but only occurred with 5% of doses.[3]

A phase II trial conducted by Kourkourakis *et al*. examined amifostine and radiotherapy in patients with thoracic cancer, head and neck cancer, and pelvic tumors. In this study the amifostine was given s.c. with a standard dose of 500 mg 20 min prior to radiotherapy. Amifostine was well tolerated by the majority of patients (85%) with nausea being the most common side effect. There was no significant hypotension. Asthenia was a problem for 5% of patients and appeared to be accumulative. Ten percent of patients suffered either a fever or rash suspected to be due to the amifostine. Typically the fever occurred 2–6 h post amifostine and lasted for 2–6 h, often with rigors, hot flushes and temperatures up to 39°C. None of the patients required hospitalization for allergic reactions.[4]

Kourkourakis *et al*. concluded there was a significant decrease in pharyngeal, esophageal and rectal mucositis for patients treated with amifostine with longer delays in radiotherapy due to grade 3 mucositis in those on the non-amifostine arm. Amifostine was also reported to decrease acute perineal skin and bladder toxicity.[4]

The American Society of Clinical Oncology (ASCO) guidelines suggest considering the use of i.v. amifostine 15–30 min prior to radiotherapy for head and neck cancer to decrease acute and late xerostomia. They conclude that there is currently insufficient data to recommend the routine use of amifostine to decrease mucositis. The use of amifostine may also be considered to reduce nephrotoxicity in patients receiving cisplatin. The ASCO guidelines state that there is no evidence that amifostine is tumor protective. They recommend using amifostine i.v. at a dose of 200 mg/m^2/day prior to radiotherapy and 910 mg/m^2 prior to chemotherapy, along with pretreatment antiemetics and careful blood pressure monitoring.[6]

There are two case reports in the literature of Steven–Johnsons syndrome due to amifostine;[7] however, there are no other reports of a life-threatening anaphylactoid reaction.

Conclusion

Whilst current literature does support the use of amifostine in decreasing the significant morbidity associated with xerostomia from radiotherapy for head and neck cancer, there remains the difficulty of balancing the benefits of treatment against its toxicity and cost.

Acknowledgments

We thank Dr Julie Fletcher (Pathology Department, Concord Repatriation & General Hospital) for histopathology slides and photos, and Dr Robert Loneragan (Radiology Department, Concord Repatriation & General Hospital) for CT scans.

References

1. Al-Sarraf M, Le Blanc M, Giri PG, *et al*. Chemotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomised Intergroup Study 0099. *J Clin Oncol* 1998; **16**: 1310–7.
2. Dorr RT Holmes BC. Dosing considerations with amifostine: a review of the literature and clinical experience. *Semin Oncol* 1999; **26**(suppl 7): 108–19.
3. Brizel D, Wasserman T, Henke M, *et al*. Phase III randomised trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol* 2000; **19**: 3339–45.
4. Koukourakis M, Kyrias G, Kakolyris S, *et al*. Subcutaneous administration of amifostine during fractionated radiotherapy: a randomised phase II study. *J Clin Oncol* 2000; **18**: 2226–33.
5. Capizzi R. The preclinical basis for broad-spectrum selective cytoprotection of normal tissues from cytotoxic therapies by amifostine. *Semin Oncol* 1999; **26**(suppl 7): 3–21.
6. Hensley M, Schuchter L, Lindly C, *et al*. American Society of Clinical Oncology Clinical practice guidelines for the use of chemotherapy and radiotherapy protectants. *J Clin Oncol* 1999; **17**: 3333–5.
7. Atahan IL, Ozyar E, Sahin S, Yildiz F, Yalcin B, Karaduman A. Two cases of Stevens–Johnson syndrome: toxic epidermal necrolysis possibly induced by amifostine during radiotherapy. *Br J Dermatol* 2000; **143**: 1072–3.

(Received 8 November 2001; accepted 10 December 2002)