KAPOSI'S SARCOMA OF THE LUNG—REMISSION FOLLOWED BY FATAL PNEUMONITIS AFTER VINBLASTINE AND THORACIC IRRADIATION

Kaposi's sarcoma (KS) with initial lung involvement is reported most often in immunocompromised patients, running a short fatal course, and the effects of treatment are not well described (1, 2). We now report an immunocompetent patient with KS limited to the lung, who responded to vinblastine and thoracic irradiation but after 10 months developed a fatal treatment-related pneumonitis.

Case report. In October 1991, a 66-year-old man presented with persistent cough, minimal sputum, slight fatigue, and increasing hemoptysis. Investigations revealed bilateral lung infiltrates, a positive 15 mm Mantoux skin test, and negative results for immune and bacterial lung disease. Left-sided thoracotomy showed multiple nodules on the surface of the lung, and biopsy of the lingula was diagnostic for KS (Figure). No lesions of KS were seen on skin, oral, trachebronchial or anorectal mucosa. There was no past history of homosexual relations, of intravenous drug use, or immunosuppressive drugs. He had had a blood transfusion 18 years before. A test for human immunodeficiency virus was negative.

In January 1992, the patient began treatment with intravenous vinblastine, 10 mg weekly. After 3 months, cough and hemoptysis resolved, chest x-rays and CT were normal, and chemotherapy was stopped. Over the next 5 months, both cough and hemoptysis recurred, and chest x-rays and CT showed gradual relapse of bilateral lung infiltrates. During August 1992 he developed severe dyspnea and stridor. On bronchoscopy there was a large obstructing tumor in the right main stem bronchus expanding into the trachea. He underwent repeated bronchoscopies with removal of 'tumor' and clots. Due to acute deterioration, radiation to the entire thoracic cavity was given, with anterior and posterior parallel fields, to a total dose of 20 Gy in 10 fractions, with a boost of 6 Gy to the right main stem bronchus. The day radiation was completed the patient restarted weekly vinblastine chemotherapy. Three weeks later he had one YAG laser treatment to the bronchial lesion, and on later endoscopies the tumor had regressed leaving a localized ulcer. Afterwards he felt well, had no cough or hemoptysis, and the chest x-ray appeared normal.

Two months later, in November 1992, the patient quickly developed cough, sputum, low-grade fever, and then severe dyspnea requiring hospitalization. Chest x-ray showed bilateral patchy infiltrates but on bronchoscopy there was only a bronchial ulcer. Arterial blood gases revealed pH 7.49, Pco2 29, Po2 52, and oxygen saturation of 88%. FVC was 2.06 l, and FEVI 1.7 l, at 50% of predicted values. A right video-thoracoscopy revealed the lung to be nodular and edematous; a wedge biopsy of the right lower lung demonstrated focal organizing intraalveolar exudate, pulmonary edema and hemosiderosis, but no evidence of infection or KS. All bacteriological, fungal, Pneumocystis carinii and viral investigations of blood, urine, bronchoalveolar lavage and lung tissue were negative, both by direct examination, culture and antobody titers. The clinical impression was interstitial pneumonitis, recurrent KS, or an adverse reaction to vinblastine or radiation. The patient was treated with wide spectrum antibiotic coverage, and corticosteroids. He required mechanical ventilation with increased ventilatory pressure, and oxygen concentrations up to 100%, to maintain arterial Po2 between 60 to 80 mm Hg. Repeated chest x-rays revealed no changes. On November 21st 1992 the patient died. Autopsy revealed no evidence of KS or infection in the lungs or elsewhere. The lungs showed the acute and organizing phases of diffuse alveolar damage.

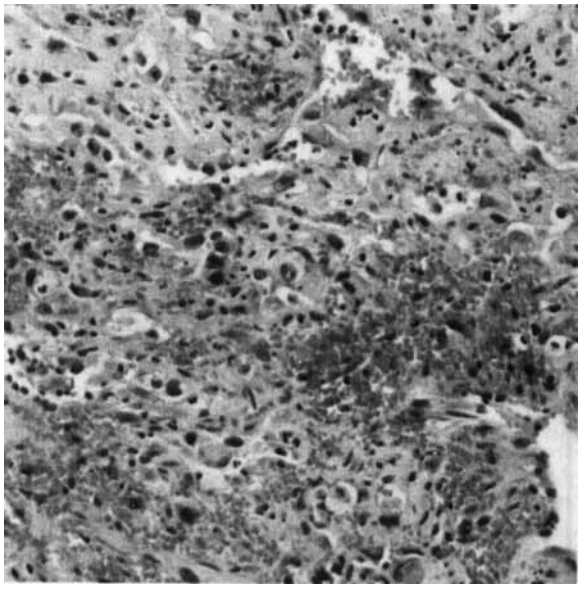

Figure. Histologically the nodules were located just under the pleura, in the interlobar fibrous septa, and along the pulmonary vessels. The malignant epithelioid cells contained cytoplasmic PAS-positive hialine bodies, Weibel-Palade bodies on electron microscopy, and they were positive for factor VIII on immunohistology.

Discussion. This immunocompetent patient with primary KS of the lung responded to vinblastine chemotherapy but relapsed shortly after discontinuation of the drug. A course of lung irradiation, laser treatment of the bronchial lesion, and vinblastine chemotherapy induced a second remission of the disease. Both vinblastine (1, 2), lung irradiation (1–6), and laser therapy (1, 2) are known to induce improvements in patients with KS of the lungs but a complete remission of the disease as in this case has not been previously reported. Within two months of the last remission, the patient developed a progressive interstitial lung process, the cause of which could not be determined either during life or at autopsy. The development of this pneumonitis following lung irradiation and vinblastine administration, suggests these therapies as the causative agents.

Vinblastine lung toxicity has been occasionally described, but all the previously reported cases also received other drugs, such as mitomycin C, which has a known propensity to cause lung damage (7). Therefore, vinblastine appears to be more a contributing rather than a direct cause of lung toxicity. Irradiation of both lungs can cause acute pneumonitis, usually within 2 or 3 months of treatment, and it may be fatal (8). The severity of the lung injury depends on the total dose, the dose per fraction, and the dose rate of radiation (8). Based on experimental and clinical observations, irradiation regimens have been developed which cause $<5\%$ rate of pneumonitis (9, 10). These regimens vary from 8 Gy single dose, to 25 Gy in 10 fractions over 13 days (9). In our patient we elected to use a course of lung irradiation of 20 Gy in 10 fractions over 2 weeks. The likely cause of his pneumonitis is lung irradiation. The severity and promptness of radiation pneumonitis, in patients receiving total body irradiation in preparation for bone marrow transplant, is related to preexisting lung abnormalities, advanced age, graft-versus-host disease, and concurrent or sequential use of chemotherapy (11). Our patient clearly had KS affecting the lung, a relatively advanced age, and received chemotherapy sequentially to radiation.

KS has been demonstrated to predispose skin and mucous membranes of irradiated areas to unexpected severe reactions (12, 13). Chemotherapy and radiation often have additive effects on local tissues (8): in an AIDS patient with KS, a vinblastine-induced recall reaction occurred in the previously irradiated skin of the lower extremities (14). These observations indicate that KS by itself may be a predisposing factor for the toxic drug-radiation interaction in the skin. Such interaction in the lung would be more difficult to recognize, because its clinical picture may be interpreted as progression of the disease. Only a pathological examination of the lung, as in our case, may definitely rule out other causes.

In summary, a patient with classical KS confined to the lung initially responded completely to vinblastine therapy and then to bilateral lung irradiation followed by vinblastine, but eventually developed a progressive pneumonitis, unresponsive to corticosteroids. Because radiation-induced lung toxicity may be facilitated by the underlying KS and concurrent chemotherapy, the usual dose of whole lung irradiation may require a downward adjustment.

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ACCIDENTAL DOXORUBICIN OVERDOSAGE

Accidents involving administration of cytostatic drugs are rare. The most common incident is extravasation, occurring in 1–6% of delivered doses (1). Other possible adverse events are overdosage and mistaken route of administration. However, when they occur it is essential to observe and report side-effects and the possibilities of treating and minimising these negative effects as well as anti-tumour effects. Anthracyclines are among the most commonly used cytostatic agents. With conventional doses their acute side-effects are mainly myelosuppression and mucositis. Their cardiac toxicity is well documented and the recommended maximum cumulative dose is at present 550 mg/m^2 (2–4). During the past decade more aggressive chemotherapy regimens have been adopted, with dose escalation and stem cell rescue. Increasing single doses of anthracyclines have been used in an attempt to improve the response rate and remission duration (5, 6). The maximum single dose as far as we are aware has been 150 mg/m^2 (epirubicin) (7). This report describes the acute toxicity in two patients who accidentally received 540 mg of doxorubicin as a single dose and 300 mg during 2 days respectively. The effect of charcoal filtering to eliminate doxorubicin is also described.

Case 1. A 58-year-old man with a history of chronic alcoholism and coronary heart disease was admitted to the emergency room with abdominal pain and coffee-ground vomiting. After initial surgical attention, the laboratory examination revealed a haemoglobin level of 62 g/l and a WBC of 41.2 × 10^9/l with 22.6% blasts in a peripheral smear. Platelets were 20 × 10^9/l. Bone marrow examination confirmed the diagnosis of acute lymphoblastic leukemia (blast count 82%). Due to deteriorated general condition cytostatic treatment was postponed. He developed mental confusion, delirious symptoms and a heavily deranged electrolyte balance including hypercalcaemia (3.8 mmol/l). After 11 days of hydrocortisone therapy (7.0 g), the patient was normocalcaemic and after 20 days he was physically and mentally alert and could be properly informed about the bone marrow disease and treatment possibilities. At this point the patient was in partial bone marrow remission (blast count 11%). Twenty-one days after admission to hospital, cytostatic treatment was initiated according to the Swedish national programme for ALL. Intrathecal treatment was omitted. Because of a series of unfortunate events, a ten-fold overdose of doxorubicin (300 mg/m^2 = 540 mg) was administered i.v. in a central line in 500 ml saline in 45 min to the patient on day 1 (Figure). Cyclophosphamide (1 100 mg) and vincristine (2 mg) were also given i.v. according to the programme and prednisone 50 mg b.i.d. orally. The accidental overdose (day 1) was observed the following morning, approximately 15 h after the infusion, and further chemotherapy was stopped. After discussion with the drug company (Farmitalia Carlo Erba, Täby, Sweden),