PULMONARY LESIONS ASSOCIATED WITH BLEOMYCIN THERAPY IN MALIGNANCIES

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ABSTRACT

Pulmonary lesions in seven patients with malignancy who were treated with bleomycin were studied at autopsy. Six of them had symptoms of respiratory distress. The lesions showed a predilection for the lower lobe and subpleural zones. Diffuse alveolar damage progressing to interstitial pneumonitis at varying stages of evolution was observed in all cases. The changes included intra-alveolar proteinaceous exudate, extensive interstitial fibrosis and frank epithelial dysplasia simulating metastatic nodules.

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KEY WORDS : Bleomycin; Diffuse alveolar damage; Interstitial pneumonitis.

Introduction

Bleomycin, an antineoplastic, antibacterial drug was first isolated from *Streptomyces verticillus* by Umezawa in 1965 [1]. It is a basic peptide of molecular weight 1400. The cystostatic effect on tumor cells is due to inhibition of thymidine incorporation in DNA and RNA synthesis [2] or single and double stranded breaks in DNA [3]. Bleomycin is now being used for treatment of a wide range of malignancies like high grade non-Hodgkin's lymphoma; squamous cell carcinoma of the head, neck, esophagus and skin; testicular carcinoma; Hodgkin's disease (as part of a combination regime); and oropharyngeal carcinoma.

Bleomycin has a distinctive advantage of no hemopoietic toxicity or immunosuppressive action, due to the presence of bleomycin inactivating enzyme in the marrow, gastrointestinal tract and other organs except the lungs and skin [2,3]. The lungs and skin are therefore, the organs of highest concentration and targets of maximum toxicity. It has been reported that 5-10% of patients receiving bleomycin develop pulmonary toxicity [4], while several have died of respiratory insufficiency [2].

The pulmonary toxicity is cumulative, approaching an overall mortality of 10% in those administered more than 450 mg/m² [3,5]. Various morphological abnormalities in these patients have been reported [5,6]. Bleomycin had also been reported to potentiate the pulmonary toxicity of methotrexate [7]. Radiation therapy and oxygen therapy further potentiate bleomycin toxicity.

Material and Methods

This retrospective study was carried out at the Department of Pathology, AFMC, Pune during the period January 1992 - December 1992. Autopsy specimens and clinical records from seven patients who had been treated with bleomycin, either alone or on combination regimes and who had suffered pulmonary toxicity symptoms ante-mortem were available for examination. Autopsies and clinical data of seven age matched patients with malignancy who did not receive bleomycin or any of the antineoplastic agents known to cause pulmonary toxicity were reviewed as controls.

The lung specimens obtained at autopsy were fixed in 10% formal saline, sectioned at 2 cm intervals for gross inspection, followed

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by multiple 3 μ m sections for histologic study. The sections were stained with hematoxylin and eosin and Gomori's methenamine silver stains.

Results

The clinical and pathological features of the patients are shown in Table 1. All of them were males with a mean age of 38.6 years. They were treated with bleomycin in a total dose ranging from 160 mg - 400 mg/m². One patient, in addition, received methotrexate. Radiotherapy was administered along with bleomycin in three patients. Six of the patients developed respiratory symptoms and died of respiratory distress. One patient with high grade intra-abdominal non-Hodgkin's lymphoma died consequent to intestinal obstruction. Pulmonary function tests, available in two of the six patients (Case Nos 1,6) with respiratory distress, showed features of hypoxic hypoxemia. Diffuse small homogenous opacities were observed radiologically in case no. 1. In the control group none of the patients died of respiratory complications

and their autopsies did not reveal lung lesions suggestive of diffuse alveolar damage or interstitial pneumonitis.

On gross examination, the lungs varied in appearance. In early disease (Cases 4,5,7) the lungs were airless, rubbery, weighing between 400-700 gms. Cut surfaces showed focal pleural thickening. The lungs of patients with advanced disease (Cases 1-3,6) showed more definite diffuse subpleural thickening, with multiple, discrete, 1 cm diameter, whitish nodules predominantly subpleural in location. The predilection for the lower lobe and subpleural zones was noted on both sides. One specimen showed honey-combing with fibrosis in the left lower lobe.

Histologically the common features observed in all cases were intra-alveolar accumulation of eosinophilic material and desquamated cells resembling macrophages or type-II pneumocytes (Fig. 1). Alveolar septae were diffusely broadened by edema fluid, focal fibrosis and mononuclear inflammatory infiltrate. The lining alveolar cells showed

TABLE 1
Clinical and pathological features in patients treated with bleomycin

Case No.	Age Sex	Tumour type	Bleomycin mg*	Other therapy	Mode of death	Histopathology
1.	29M	Nasopharyngeal carcinoma	250	Cisplastin, Steroid, RT	Respiratory distress	DAD, IP Subpleural deposits
2.	32M	NHL-high grade intra-abdominal	300	Methotrexate, Laparotomy	Intestinal obstruction	IP
3.	48M	Hodgkin's disease IV B	250	Vincristine Cisplastin Procortazine, Prednisolone	Respiratory distress	DAD, Pleural fibrosis
4.	49M	Seminoma testis	160	Cisplastin Vinblastine	Respiratory distress	DAD
5.	32M	Embryonal carcinoma testis	400	Etoposide Cisplastin Cranial RT	Respiratory distress	DAD, IP
6.	38M	Hodgkin's disease	250	Adriamycin Vinblastine Chlorambucil	Respiratory distress	Honeycombing
7.	42M	Anaplastic carcinoma pharynx	250	Cisplastin RT	Respiratory distress	DAD, IP

* Total dose per sq. metre body surface area, RT - radiotherapy, DAD - diffuse alveolar damage, IP - interstitial pneumonitis.

Fig. 1 : Intra-alveolar eosinophilic material, desquamated cells and inflammatory cells. H & E, 150x.

Fig. 2 : Interstitial fibrosis with loss of alveolar spaces. H & E, 40 x.

stratification and revealed abundant, well defined cytoplasm, irregular nuclei with prominent nucleoli. The sections from patients with advanced disease showed extensive interstitial fibrosis with loss of alveolar spaces (Fig. 2). This was prominent in continuity with the subpleural zones. Entrapped in these subpleural fibrotic areas were patterns at places resembling secondary deposits (Fig.3). These cells were pleomorphic with hyperchromatic nuclei and focal squamous metaplasia (Fig. 4). Some of the alveolar spaces contained a polymorphous inflammatory infiltrate in addition to focal areas of bronchopneumonic consolidation (Cases 2,6). Vascular channels, especially veins showed fibrosis. No granulomas or opportunistic organisms were seen. The above mentioned changes were collectively termed as diffuse alveolar damage and interstitial pneumonitis. No skin toxicity was observed in these cases.

Discussion

Chemotherapeutic agents especially busulfan, bleomycin and methotrexate are known to cause pulmonary toxicity. The rate of bleomycin induced pulmonary toxicity is 5-10% [4]. When used in combination with methotrexate, it potentiates the toxicity of the latter. The incidence of pulmonary toxicity in

Fig. 3 Subpleural fibrotic nodule with dysplastic epithelial cells in pseudoglandular pattern. H & E, 150x.

Fig. 4 Stratified pleomorphic cells with squamous metaplasia. H & E, 600x.

non-Hodgkin's lymphoma patients on combination regime of bleomycin and methotrexate has been estimated to range between 0-18% [7].

The reaction to bleomycin has now been established to be directly related to the cumulative dosage administered. Various studies have reported pulmonary toxicity when the dosage exceeded 200 mg/m² [9]. Definite increase in the risk of pulmonary toxicity has been documented in patients receiving more than 500 mg/m², while a linear correlation between pulmonary interstitial fibrosis and increasing dosage has been demonstrated [10]. Concurrent radiotherapy and positive-pressure intermittent oxygen administration potentiate the effects of bleomycin [11]. The features of bleomycin toxicity may appear between two weeks to six months after initiation of therapy and may lead to a fatal outcome several weeks after the withdrawal of the drug. Radiologically diffuse linear interstitial opacities are characteristic and may either disappear or appear on cessation of therapy [12-14]. Significant reactions are known to develop after cessation of bleomycin. Steroids are considered useful in resolving or arresting the changes. The highest concentration of bleomycin is found in the lungs and hence the maximal toxicity [3]. The histologic findings in the lungs of bleomycin treated patients are non-specific and represent the final common pathway for the action of many agents upon the air-blood membrane. The changes observed are collectively called diffuse alveolar damage progressing to interstitial pneumonitis. These changes are also observed in busulfan and methotrexate toxicity. However, the honey-combing and subpleural lower lobe location of the lesions is characteristic of bleomycin toxicity, the reasons for it being unclear. Diffuse interstitial intra-alveolar desquamation of cells and epithelial hyperplasia are other features seen in 'bleomycin lung'. The subpleural nodules on histologic examination simulate metastatic nodules [14].

The other conditions which are responsible for acute interstitial pneumonitis in such

clinical settings are of viral etiology. These lesions are essentially focal and anatomically related to bronchioles unlike the diffuse changes seen in bleomycin toxicity.

Administration of bleomycin alone or in combination with other potentiating agents like methotrexate, irradiation and oxygen therapy must be followed up with periodic assessment of pulmonary function and radiologic review to aid early detection and possible prevention of bleomycin toxicity.

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