Uncommon manifestation of bleomycin-induced pulmonary toxicity in a patient with Hodgkin’s disease

Bleomycin is an antitumor antibiotic isolated from a strain of *Streptomyces verticillus* in 1966. It has been used successfully to treat a variety of tumors, including squamous cell carcinoma of the head and neck, cervix, and esophagus, as well as germ cell tumors and Hodgkin’s and non-Hodgkin’s lymphomas. The major limitation of bleomycin therapy is the potential for developing life-threatening pulmonary toxicity, which most commonly takes the form of interstitial pneumonitis. Nevertheless, other forms of lung injury have also been reported, although less commonly [1]. We report the case of a patient who received bleomycin and subsequently developed an uncommon manifestation of pulmonary toxicity.

A 24-year-old female patient was diagnosed with nodular sclerosing Hodgkin’s disease in January 2002. Cervical and mediastinal lymphadenopathy were identified; the patient was staged as IIB and was treated with a combination of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD). A computed tomography (CT) examination of the chest obtained after three cycles of ABVD revealed development of bilateral, peripheral, poorly defined areas of focal consolidation and bronchial wall thickening, and at the same time significant amelioration of the pre-existing mediastinal lymphadenopathy (Figure 1). The patient was completely asymptomatic and afebrile, while routine laboratory investigation was within the normal limits. Extensive work-up, including bronchoalveolar lavage, in order to identify a possible infectious cause of the pulmonary infiltrates yielded negative results. The patient was empirically treated with multiple antimicrobial, antituberculous and antifungal agents without any improvement of the radiological findings. Transthoracic needle aspiration biopsy disclosed sparse infiltration with inflammatory cells and a few hyperplastic pneumocytes; no evidence of malignancy or infection was identified. The radiological findings were attributed to bleomycin toxicity and resolved spontaneously and completely 2 months after cessation of its administration. Subsequently, the patient was treated with three cycles of a non-bleomycin-containing regimen [chlorambucil, vinblastine, procarbazine and prednisone (ChlVPP) combined with etoposide, vincristine and adriamycin (EVA)] and achieved a complete remission, which is sustained after a follow-up of 15 months.

Bleomycin is inactivated *in vivo* by bleomycin hydrolase, a cytosolic aminopeptidase. This enzyme is active in all tissues with the exception of the skin and the lung, which may account for the specific toxicity of the drug to these organs [2]. The mechanisms of bleomycin-induced lung injury are not entirely clear. The acute pulmonary toxicity of bleomycin has been attributed to DNA strand scission [3]. Several factors, including age, drug dose, renal function, concomitant use of oxygen, radiation therapy and a smoking history, may increase the risk of developing bleomycin lung toxicity [4]. Although administration of higher doses of bleomycin clearly increases the risk of lung injury, injury can occur at doses <50 mg. The patient described here received a cumulative bleomycin dose of 90 mg/m², and none of the other clinical factors predisposing to lung toxicity were present.

Unlike patients with bleomycin-induced pneumonitis, patients with other pulmonary syndromes can be asymptomatic at presentation [5]. Bleomycin-induced alterations may appear earlier on CT than on chest radiographs [4]. Differentiation of these findings from manifestations of the primary disease can be difficult, and biopsy may be required [5].

There are no studies demonstrating the efficacy of therapy for bleomycin-induced lung injury in humans. Corticosteroids are widely applied when bleomycin-induced pulmonary toxicity occurs, but data supporting their efficacy is scarce [4]. We did not administer corticosteroids in our patient, since the diagnosis was uncertain and the radiological findings showed gradual improvement; nevertheless, we decided to withhold further bleomycin administration and applied a non-bleomycin-containing regimen after the complete resolution of the pulmonary infiltrates.

In conclusion, pulmonary toxicity is a frequent and sometimes severe side-effect of bleomycin. Its manifestations are variable and the clinician should be able to promptly identify...
and differentiate them from other conditions in order to institute the appropriate treatment, if this is possible. 

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Fludarabine: risk factor for aggressive behaviour of squamous cell carcinoma of the skin?

Fludarabine, a purine analogue, is effective in the therapy of low-grade non-Hodgkin’s lymphomas. Side-effects include fever, peripheral neuropathy, pulmonary toxicity and significant depletion of T-lymphocyte populations. In addition, flare up and aggressive behaviour of squamous cell carcinoma (SCC) during fludarabine therapy has been observed [1].

We report on a 65-year-old patient with a lymphocytic B-cell lymphoma (stage IVA) diagnosed in 1997. Owing to an excess of blasts he was treated according to the German consensus protocol for aggressive non-Hodgkin’s lymphoma. However, three cycles of CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone) chemotherapy and two cycles of salvage therapy with holoxane, cytosar and vepeside did not produce a response, and led to complications such as Candida esophagitis and generalised herpes zoster infection. Owing to progressive lymphadenopathy and lymphocytosis, the patient was treated with four cycles of chlorambucil and prednisone, showing again minimal response. In 2001, six cycles of fludarabine led to a near complete remission with reduction of all lymph node manifestations and normalisation of peripheral lymphocyte counts. Since the patient’s disease progressed again, a combined immunochemotherapy with rituximab and fludarabine was initiated in autumn 2002. Again, a near complete clinical remission was achieved. However, within 2 weeks of the fourth therapy cycle, the patient developed a well-circumscribed nodule on the right cheek. The tumour impressed with a diameter of 1 cm and a centrally located horn plug.

Histology showed a well demarcated invasive proliferation of epithelial cells with squamous differentiation, extending into the dermis, a perineural invasion by tumour cells and lymphohistiocytic infiltration at the margins of the neoplasm. Immunohistochemistry revealed that the majority of the infiltrating lymphocytes were CD3+ CD4+ T-helper cells, whereas a few cells expressed CD8 antigen. Complete excision of the lesion was conducted and confirmed by micrographic work-up of the specimen. Two months later the patient presented with regrowth of the tumour. Again, total excision was performed resulting in two further recurrences within the following 3 months. Nine months after local consolidating radiotherapy (51 Gy) no further recurrence had occurred.

Although differential diagnosis of keratoacanthoma was considered initially, the histological features of perineural invasion and infiltrative tumour strands, as well as repeated tumour recurrence, strongly suggested the diagnosis of SCC [2, 3]. However, aggressive behaviour of the tumour led to the question of whether in this immunocompromised patient human papilloma viruses (HPV), especially HPV 5 and 8, might be involved in the development and unusual clinical course of skin cancer [4]. Accordingly, we performed a nested PCR, but did not detect the suspected HPV-specific sequences in the biopsy tissue. Non-Hodgkin’s lymphomas on their own or fludarabine may be responsible for the increased incidence and aggressive behaviour of SCC in these patients [5]. Thus, we assume that the altered immune status in this patient was aggravated by concomitant fludarabine-induced T-lymphocyte depletion, which thereby facilitated the growth and aggressive behaviour of this secondary malignancy [6]. Careful examination of patients at risk will be warranted in order to detect secondary malignancies early and to treat them extensively.

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