

# Toxicities associated with bleomycin

<sup>1</sup>AJ Fyfe, <sup>2</sup>P McKay

<sup>1</sup>Specialist Registrar in Haematology; <sup>2</sup>Consultant Haematologist, Gartnavel General Hospital, Glasgow, UK

**ABSTRACT** Bleomycin is an anti-neoplastic antibiotic used in chemotherapeutic regimens for Hodgkin lymphoma, testicular tumour and Kaposi's sarcoma and to induce chemical pleurodesis in malignant effusions. Bleomycin toxicity predominantly affects the skin and lungs. Skin toxicity classically presents as flagellate erythema, a rare drug rash, where the patient appears to have been whipped. Bleomycin-induced pneumonitis is more commonly recognised and can occasionally prove fatal. Although both these conditions are well documented in the literature, in clinical practice they are uncommon. Indeed, in our institution (a teaching hospital with a large lymphoma practice) we cannot recall a previous case of flagellate erythema. Both skin and lung toxicities induced by bleomycin usually respond to discontinuation of the drug and steroid therapy. We present two case studies of patients with bleomycin-related toxicity and a short synopsis of current literature.

**KEYWORDS** ABVD chemotherapy, bleomycin, flagellate erythema, Hodgkin lymphoma, pneumonitis

**DECLARATION OF INTERESTS** No conflict of interests declared.

## CASE REPORT I

A 47-year-old woman was diagnosed with Stage IIIB Hodgkin lymphoma (HL). There was no medical history of note and specifically no history of dermatological disorders or allergy. She was commenced on adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy, given on days 1 and 15 of each course. After 34 days from the start of treatment she developed an erythematous linear rash that was most prominent on her anterior chest, neck, upper back and shins (Figures 1–3). There was no evidence of mucosal involvement or systemic upset. The patient was referred promptly to the dermatologists.

A diagnosis of flagellate erythema due to bleomycin was made. The patient was commenced on a short course of oral prednisolone, 40 mg daily, and topical betamethasone valerate, applied twice daily to the affected areas. The erythematous component of the rash settled within three weeks, leaving residual areas of hyperpigmentation, itch and scaling. No further bleomycin was administered. She continued with AVD and received a total of six cycles of chemotherapy.



**FIGURE 1** Flagellate erythema affecting the chest wall.



**FIGURE 2** Flagellate erythema affecting the lower legs.



**FIGURE 3** Associated skin changes on the palmar surfaces.

**Correspondence to** AJ Fyfe,  
Laboratory Buildings, Gartnavel  
General Hospital, Great Western  
Road, Glasgow G12 0XB, UK

tel. +44 (0)141 301 7730  
e-mail [andrew.fyfe@nhs.net](mailto:andrew.fyfe@nhs.net)

## CASE REPORT 2

A 64-year-old man was diagnosed with Stage IIB mixed cellularity HL. The patient was a long-term pipe smoker but had no symptoms of chronic pulmonary disease. Pulmonary function tests carried out shortly after diagnosis were normal. He received six cycles of ABVD uneventfully, achieving complete remission. Two weeks after the completion of chemotherapy he developed a dry cough and worsening exertional dyspnoea. His chest was clear to auscultation and oxygen saturation was 98% on room air. A chest X-ray revealed bilateral basal consolidation in keeping with an infective process, and the patient was commenced on antibiotics with no symptomatic improvement. A computed tomography (CT) scan revealed diffuse patchy pulmonary opacification with fibrotic changes at both lung bases (Figure 4). A provisional diagnosis of bleomycin-induced pulmonary toxicity was made. The patient was commenced on prednisolone, 60 mg daily, with a rapid clinical response. The dose of steroid was tapered and stopped over an eight-week period. At review two weeks later, his symptoms had completely resolved and his exercise tolerance had returned to normal.

## BLEOMYCIN

Bleomycin is a sulphur-containing chemotherapeutic antibiotic.<sup>1</sup> Its mode of action is to inhibit the incorporation of thymidine into deoxyribonucleic acid (DNA). Bleomycin was first developed in Japan in 1966 by Umezawa et al. It is most commonly used as part of the chemotherapy regimen ABVD – the standard chemotherapeutic regimen for HL in the UK. It is also used in the treatment of certain germ cell tumours and Kaposi's sarcoma. Bleomycin may also be used to induce chemical pleurodesis in malignant pleural effusions.<sup>2</sup>

Following administration, bleomycin is distributed around the body, with 60–70% being excreted unchanged in the urine. Patients with a reduced creatinine clearance may have a significantly reduced bleomycin clearance and this may be clinically important with regard to toxicity.<sup>1</sup> It is inactivated in most tissues by an enzyme, bleomycin hydrolase, which cleaves the ammonia group from bleomycin. This enzyme is active in all tissues except skin and lung, which may account for these being the most common sites of toxicity.<sup>1</sup>

## FLAGELLATE ERYTHEMA

Flagellate erythema is an unusual rash in which the patient appears to have been whipped over multiple body areas. It typically presents with itching, coinciding with the appearance of erythematous linear streaks which are found most commonly on the upper chest and back, limbs and flanks. As the rash becomes less erythematous, the affected areas usually become deeply pigmented. These hyperpigmented lesions can last up to six months.<sup>3</sup>



**FIGURE 4** Bleomycin-induced pulmonary fibrosis.

Flagellate erythema was first reported in association with bleomycin administration in 1970.<sup>4</sup> It may appear following administration by intravenous, intramuscular or topical routes and has been reported after the administration of the drug into an indwelling intercostal chest drain for the treatment of a malignant pleural effusion. The development of the rash appears to be dose independent and can appear following first administration.<sup>3,5</sup> A similar clinical entity, which can also be described as flagellate erythema, has been observed with the administration of bleomycin derivatives, docetaxel and the ingestion of shiitake mushrooms. It has also been described in association with adult Still's disease and dermatomyositis.<sup>6</sup>

The rash may remit spontaneously with the withdrawal of bleomycin but may, as in the illustrated cases, require topical corticosteroids with or without oral corticosteroids. Re-exposure to bleomycin may cause further extension or recurrence of this rash and should be avoided.<sup>3</sup> Bleomycin can also be associated with other dermatological toxicities. In addition, alopecia, skin ulceration (predominantly plantar-palmar), angular stomatitis, eczematous changes, erythematous bulla, sclerodermoid lesions, nail bed changes and Raynaud's phenomenon have been described.<sup>7,8</sup>

## PULMONARY TOXICITY

While flagellate erythema and other associated skin toxicities may be unpleasant or unsightly, they are not associated with increased morbidity or mortality and usually resolve on the withdrawal of the drug. The same cannot be said for bleomycin-induced pneumonitis. Although the incidence is often quoted as 6–10%, it may occur in up to 46% of patients receiving bleomycin with a mortality of 3–5% in those affected.<sup>2</sup> Symptoms of bleomycin-induced pneumonitis most commonly occur subacutely during treatment, although it has been reported to occur acutely or up to six months post treatment.<sup>9</sup> Common presenting features are cough, dyspnoea, reduced exercise tolerance and, occasionally, fever. Initially, clinical signs may be few and non-specific; in later stages there may be features of pulmonary fibrosis with fine crepitations on auscultation and reduced lung expansion.

Radiological features are variable; the typical pattern includes bibasal subpleural opacification with loss of volume. Later progressive consolidation and honeycombing is seen. High-resolution CT typically shows ground glass opacification in the mid and lower zones. Non-specific nodular densities may mimic metastatic deposits. Pulmonary function tests reveal a reduced transfer factor initially, followed by a restrictive defect as fibrosis develops. The differential diagnosis includes other forms of interstitial lung disease, infection, metastatic disease, radiation-induced damage and other drug-induced damage.

The risk of developing bleomycin-induced pulmonary toxicity is increased by a number of factors, including increasing age, higher doses of the drug, impaired renal function (creatinine clearance <35 ml/min), high concentration oxygen therapy and radiation therapy to the thorax. There are conflicting data as to whether concomitant granulocyte colony stimulating factor (G-CSF) therapy increases the risk of bleomycin-induced lung injury.<sup>10,11</sup> The evidence that full-dose ABVD can be given safely on time irrespective of the neutrophil count has led many clinicians to avoid the use of G-CSF with ABVD chemotherapy.<sup>12</sup> Our local practice changed following this publication, and an audit in 2009 confirmed their findings.<sup>13</sup>

If bleomycin-induced pneumonitis is suspected, the drug should be discontinued and attempts made to exclude infection by sputum analysis or bronchoalveolar lavage if required. Treatment is usually with oral corticosteroids, although there are no controlled studies on the use of corticosteroids in the treatment of this condition. The optimum dose and duration of treatment is also unknown; however, starting doses of 40–60 mg of prednisolone daily are often employed, although some advocate higher doses of up to 100 mg daily. Clinical response is usually in weeks rather than days and is most likely in those with a

significant inflammatory component. Doses can be tapered slowly over weeks based on clinical response, with radiological and pulmonary function improvements lagging behind. Some clinicians argue that the improvement seen with corticosteroids in small study groups may well be due to incorrect diagnoses in these patients. Bleomycin-induced pneumonitis closely resembles cryptogenic organising pneumonia, which is known to respond to corticosteroid therapy.<sup>14</sup>

Bleomycin-induced pneumonitis is thought to resolve in the majority of patients over time, with improvement in pulmonary function and radiology seen at >15 months. Complete resolution of symptoms, signs, abnormal radiology and pulmonary function tests is less likely if the diagnosis is delayed, if bleomycin therapy is continued or if established fibrosis occurs.

Although these two conditions are well described in the literature, they are not commonly seen in clinical practice. Given the potential severe morbidity and mortality associated with bleomycin-induced pneumonitis, clinical awareness is key to allow the removal of bleomycin from therapy at the earliest possible stage and limit dose-dependent toxicity. Early recognition of bleomycin-associated skin toxicity (e.g. flagellate erythema) is also important to prevent further exacerbation of the rash by continuation of therapy. Given that patients may present via acute receiving or to respiratory physicians and dermatologists, it is important that these physicians, in addition to haematologists and oncologists, are aware of the drug-associated toxicities. There is some evidence that bleomycin can be omitted from combination chemotherapy in the treatment of HL without loss of efficacy.<sup>15</sup> Research is ongoing in HL, and also in teratoma, to determine if this is the case. In the meantime, bleomycin remains in current first-line regimens for the treatment of HL.

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