

BRIEF REPORT

Busulfan associated pulmonary toxicity: A benign mimic of squamous cell carcinoma diagnosed in a bronchoalveolar lavage specimen

Suzanne M. Selvaggi MD 

Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

Correspondence

Suzanne M. Selvaggi, MD, Department of Pathology and Laboratory Medicine, Cytology/Clinical Labs/D4/259d, University of Wisconsin Hospital and Clinics, 600 Highland Avenue, Madison, WI 53792-2472, USA.
Email: sselvaggi@uwhealth.org

Abstract

An uncommon case of iatrogenic cellular changes associated with busulfan therapy in a bronchoalveolar lavage of a 65-year-old woman who underwent bone marrow transplantation is presented and discussed. Chemotherapeutic changes are presented, and pitfalls discussed.

KEYWORDS

bronchoalveolar lavage, pulmonary cytology, busulfan therapy

1 | INTRODUCTION

Iatrogenic cellular changes associated with chemotherapy are important pitfalls in the diagnosis of malignancy.¹⁻⁷ Chemotherapeutic changes are seen with several anticancer drugs including bleomycin, busulfan, cyclophosphamide, methotrexate, and amiodarone, but changes are seen most frequently with busulfan.⁷ Pulmonary side effects include diffuse alveolar damage with subsequent marked epithelial atypia.^{5,8,9}

Currently, bronchoalveolar lavage is the initial diagnostic procedure in most patients on chemotherapy who develop pulmonary infiltrates. In a study⁵ of 77 patients with bone marrow transplants and prior cytotoxic therapy, epithelial atypia was detected in BAL samples from 14 of 77 patients of which 11 had received autologous bone marrow transplants. Cellular changes included enlarged hyperchromatic nucleoli, prominent nucleoli, nuclear molding, nucleomegaly, vacuolated cytoplasm and occasional ill-defined cytoplasmic borders, features mimicking carcinoma. An interesting case of busulfan induced pulmonary cytotoxicity diagnosed on a ThinPrep prepared BAL sample from a woman with prior bone marrow transplant is reported.

2 | CASE REPORT

The patient was a 65-year-old female who presented to the University of Wisconsin Hospital mid-December 2020 complaining of shortness of breath. Her past medical history was significant for myelodysplastic syndrome (MDS) with refractory anemia and excess blasts (RAEB) type II, which required an allogenic stem cell transplant in early August 2020. Concern for an infectious versus neoplastic process prompted performance of a bronchoalveolar lavage (BAL). Further investigation of the patient's medical history and imaging revealed that prior to her bone marrow transplant, she was treated with Busulfan and Fludarabine per hematologic conditioning protocol. Additionally, the CT of the chest performed at admission revealed bilateral ground glass opacities suggestive of a diffuse lung disease with alveolar damage. A discrete lung mass was not identified, and the patient's social history was negative for tobacco use. Her hospital stay was complicated by graft-versus-host disease and worsening respiratory failure for which she was intubated and placed on ventilatory support. An infectious disease work-up revealed no causative organisms. Despite increased pressors, her cardiac status deteriorated. After discussions with the family, the patient was withdrawn from life support, and she expired on 12/16/2020. A request for autopsy was denied.

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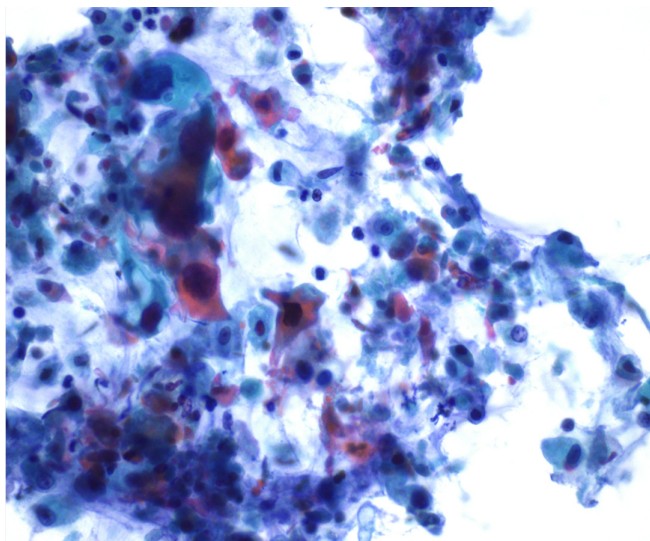


FIGURE 1 Atypical epithelial cells with enlarged hyperchromatic nuclei with smudged chromatin and orangeophilic cytoplasm with degenerated cellular debris in the background (ThinPrep; Papanicolaou stain, $\times 60$)

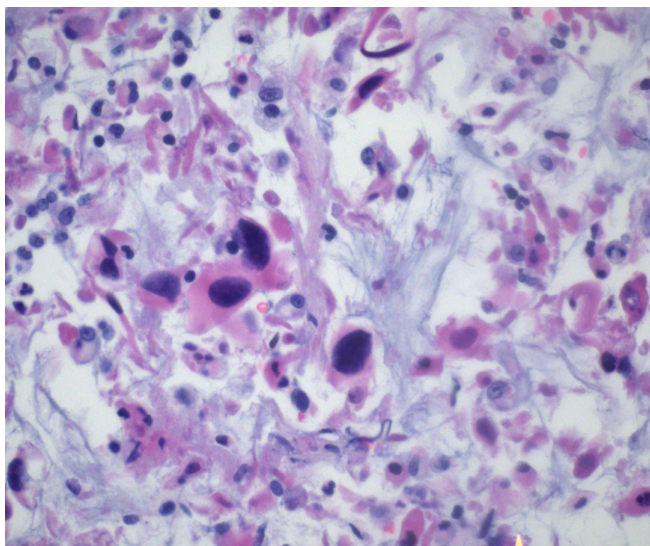


FIGURE 2 Numerous atypical epithelial cells with an increased nuclear and cytoplasmic size, some elongate in shape. The nuclei contain hyperchromatic, smudged chromatin (cell block; hematoxylin-eosin stain, $\times 60$)

3 | MATERIAL AND METHODS

From the BAL specimen both a ThinPrep slide and a cell block were prepared. The thin-layer slide was prepared using the ThinPrep 3000 automated processor (Hologic Corp.), according to the manufacturer's instructions and Papanicolaou-stained. The cell block was made utilizing the plasma-thrombin clot technique¹⁰ fixed in 10% buffered formalin and paraffin-embedded. The 3 μm thick sections were stained with hematoxylin-eosin. Immunohistochemical staining was

performed on the cell block material with the use of antibodies for CMV and Herpes 1 and 2, with the appropriate positive and negative tissue controls.

3.1 | Cytologic findings

The ThinPrep slide contained enlarged polygonal to elongate-shaped markedly atypical epithelial cells arranged singly and in clusters in a background of degenerated cellular debris (Figure 1). Nuclei contained hyperchromatic smudged chromatin, without discernable nucleoli and orangeophilic cytoplasm, findings suggestive of squamous cell carcinoma. These cellular features were also present on the cell block prepared slide (Figure 2). Immunohistochemical staining for CMV and combined Herpes 1 and 2 were negative. There was no cytological evidence of the presence of inflammatory cells, microorganisms and viral cytopathic effects. Although a diagnosis of squamous cell carcinoma was entertained, thorough review favored cellular changes consistent with Busulfan chemotherapy effect.

4 | DISCUSSION

Busulfan (Myleran) is a cell cycle non-specific alkylating antineoplastic agent, in the class of alkylsulfonates. Busulfan was approved by the US Food and Drug Administration (FDA) for the treatment of chronic myeloid leukemia (CML) in 1999 and currently is used in children and adults in combination with cyclophosphamide or fludarabine/clofarabine as a conditioning agent prior to bone marrow transplantation, especially in CML and other leukemias, lymphomas, and myeloproliferative disorders.¹¹ Toxic complications include interstitial pulmonary fibrosis ("Busulfan Lung") with diffuse alveolar damage. The average time from the initiation of treatment to the development of respiratory symptoms may range from 8 months to 10 years but may occur as early as 6 weeks from the initiation of treatment.¹² The incidence of Busulfan associated pulmonary toxicity is estimated to be 6% with a range of 2.5%–43% reported in the literature.¹¹ Chest radiographs of patients presenting with this disease process often reveal an interstitial infiltrative process in combination with an alveolar pattern often more severe than other chemotherapy-induced pulmonary reactions. This is thought to be due to significant desquamation of injured epithelial cells in alveolar spaces. Although some patients improve with administration of steroids, the majority develop progressive respiratory failure eventuating in death,⁷ as was the outcome in the case presented.

Chemotherapy can cause marked cytologic atypia in squamous or glandular cells that mimic non-small cell carcinoma. Busulfan causes worrisome alterations in squamous cells that can mimic carcinoma as marked keratinization can occur. Changes include marked cellular and nuclear enlargement, nuclear hyperchromasia with coarse chromatin, and irregular nuclear membranes, orangeophilic to pink cytoplasm and variation in the size and shape of the cells.^{2,7} Gulbahce et al.¹³ reported the presence of cytologic atypia in 27 BAL specimens from

21 bone marrow transplant recipients of which 13 had cytoreductive treatment. The atypical cells with squamous features were often single or in small cellular groups. Elongate cells contained hyperchromatic nuclei without visible nucleoli and dense orangeophilic to pink cytoplasm; cytologic features present in the current case.

In order to distinguish chemotherapy effect from squamous cell carcinoma, the following cellular features have been reported^{1-3,7-9,13} including:

1. The presence of epithelial cells in high numbers.
2. The presence of bizarre cellular changes including abundant cytoplasm and enlarged nucleus.
3. Large hyperchromatic nuclei with smudgy chromatin with little or no nuclear detail (i.e., degenerative changes).
4. Smooth nuclear borders.

Classic features of squamous cell carcinoma are distinguished from chemotherapeutic effect in this setting, primarily by nuclear detail, with squamous cell carcinoma exhibiting coarse versus "smudgy" chromatin pattern and angulated versus smooth nuclear borders. Since cellular degeneration is observed in both chemotherapy effect and squamous cell carcinoma, it is of limited value in differentiating these two entities. Finally, as no one feature is uniquely diagnostic, the importance of radiographic findings, clinical and therapeutic history cannot be overemphasized when trying to avoid the diagnostic traps in mimics of malignancy.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Suzanne M. Selvaggi  <https://orcid.org/0000-0002-7248-0782>

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