

## CASE STUDY

# Bronchiolitis obliterans organizing pneumonia in three children with acute leukaemias treated with cytosine arabinoside and anthracyclines

E. Battistini\*, G. Dini\*\*, C. Savioli<sup>+</sup>, A. Morando<sup>+</sup>, A. Gandolfo<sup>++</sup>,  
Z. Kotitsa<sup>++</sup>, A. Garaventa<sup>\*\*</sup>, G.A. Rossi\*

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**ABSTRACT:** Bronchiolitis obliterans organizing pneumonia (BOOP) is a clinico-pathological entity with well-defined diagnostic criteria, which can be idiopathic or produced by a variety of biological processes. We describe the occurrence of BOOP in three children, one with acute lymphoblastic leukaemia and two with acute promyelocytic leukaemia.

In the three patients, BOOP developed 10–20 days after a course of therapy with cytosine arabinoside and anthracyclines. The possible relationships between the small conducting airway lesions, lung toxic reaction to the drugs and/or nonidentified infectious agents are discussed.

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Divisione di \*Pneumologia and \*\*Medicina 4, +Servizi di Anatomia Patologica and ++Anestesiologia e Rianimazione, Istituto G. Gaslini, Genoa, Italy.

Correspondence: E. Battistini, Division di Pneumologia, Istituto G. Gaslini, Largo G. Gaslini 4, 16148 Genova, Italy

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Bronchiolitis obliterans organizing pneumonia (BOOP) is a relatively uncommon fibrotic lung disease, characterized histologically by the presence of: 1) patchy inflammatory changes of the bronchoalveolar lumen and wall, with some associated peribronchiolar scarring; 2) patchy areas of organizing pneumonia; 3) obliteration of the airway lumen by intraluminal polyps of loose connective tissue, containing inflammatory cells and fibroblasts; and 4) an interstitial mononuclear cell infiltrate, of variable density [1–3]. These changes, which involve mainly the respiratory bronchioles and the alveolar ducts, are thought to represent intraluminal organization of persistent bronchoalveolar exudate by fibroblasts and capillaries from the bronchial and alveolar walls [2, 3]. BOOP can be idiopathic or can be produced by a variety of immunological, toxic and inflammatory processes [1–10]. In addition, BOOP has been reported in patients with myelodysplastic syndromes [11–12], with irradiation pneumonitis [13], and following administration of different drugs [14–20]. We describe the cases of three patients, one with acute lymphoblastic leukaemia and two with acute promyelocytic leukaemia, who develop-

ed BOOP 10–20 days after a course of chemotherapy with cytosine arabinoside and anthracyclines.

## Case reports

The three female patients (Nos. 1–3) were, respectively, 6, 9 and 12 yrs of age (table 1). The underlying diseases were acute lymphoblastic leukaemia (ALL) in patient No. 1, and acute promyelocytic leukaemia (APL) in patients Nos. 2 and 3.

### Patient No. 1

Patient No. 1 had ALL diagnosed 11 months before evaluation and was treated with a protocol which included the administration of five courses of vincristine and daunorubicin (DNR). One month before evaluation, the patient experienced ALL relapse and was treated with idarubicin (IMI-30), 12 mg·m<sup>-2</sup> *i.v.*, daily for 3 days, and cytosine arabinoside (ARA-C), 3 g·m<sup>-2</sup> *i.v.*, daily for 3 days.

Table 1. – Characteristics of patients with bronchiolitis obliterans organizing pneumonia (BOOP)

Pt No.	Sex	Underlying disease	Therapeutic agents	Time <sup>#</sup> to onset of BOOP days	Symptoms
1	F	ALL	IMI-30, ARA-C	20	Fe
2	F	APL	DNR, ARA-C	20	Fe, C, N
3	F	APL	DNR, ARA-C	10	Fe, D, N

<sup>#</sup>: from last therapeutic course. F: female; ALL: acute lymphoblastic leukaemia; APL: acute promyelocytic leukaemia; IMI-30: idarubicin; ARA-C: cytosine arabinoside; DNR: daunorubicin; Fe: fever; C: cough; N: severe neutropenia; D: dyspnoea.

After 20 days, the patient presented with fever ( $>38^{\circ}\text{C}$ ) and leucopenia (white blood cell (WBC) count  $0.5 \times 10^9$  cells $\cdot\text{L}^{-1}$ ). Body fluid cultures were negative, and the patient was empirically treated with ceftazidime, amikacin and amphotericin B, with no clinical response. Chest radiographs and computed tomography (CT) scans showed a pulmonary infiltrate in the posterior segment of the upper right lobe (fig. 1). Fiberoptic bronchoscopy was performed: bronchoalveolar lavage (BAL) demonstrated a mild increase in the percentage of neutrophils (4%), and lymphocytes (12%), as compared to normal reference values in our laboratory ( $0.1 \pm 0.2$  and  $7.1 \pm 0.6\%$ , respectively) [21]. Standard cytological, cultural and molecular biology tests performed on BAL materials for detection of fungi, mycobacteria, *Pneumocystis carinii*, Epstein Barr virus (EBV) and cytomegalovirus (CMV) were all negative.

Roentgenographic re-evaluation of the patient 10 days later demonstrated the appearance of a new pulmonary lesion in the lower portion of the right lung and a small cavitation in the context of the primary infiltrate. Open lung biopsy was performed and showed intraluminal buds of granulation tissue in the distal airspaces, in the



Fig. 1. – Chest computed tomography of the lung lesion in patient No. 1, demonstrating a pulmonary infiltrate in the posterior segment of the upper right lobe, without pleural effusion or lymph node enlargement.

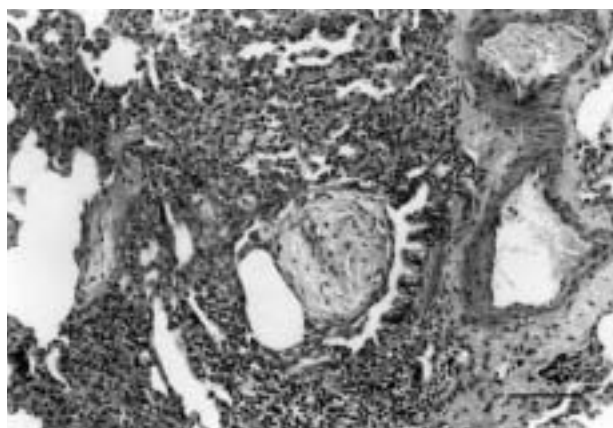


Fig. 2. – Morphological evaluation of the open lung biopsy sample from patient No. 1, showing inflammatory changes of the distal airspaces, characterized by interstitial collection of mononuclear cells. These changes are associated with intraluminal buds of loose connective tissue containing inflammatory cells and fibroblasts (haematoxylin and eosin stain internal scale bar = 200  $\mu\text{m}$ ).

context of focally collapsed alveoli and of a mononuclear cell alveolitis (fig. 2). Following surgery, the patient had a complete clinical and roentgenographic recovery.

#### Patient No. 2

Patient No. 2 was affected by APL and treated with DNR and ARA-C. After 1 month, because of persistence of disease at bone marrow level, she underwent chemotherapy with IMI-30, 10  $\text{mg}\cdot\text{m}^{-2}$  daily for 6 days.

Twelve days later, the patient complained of fever and cough. The WBC count was  $0.12 \times 10^9$  cells $\cdot\text{L}^{-1}$ . Since blood and urine cultures were negative, the patient was empirically treated with ceftazidime, vancomycin and amphotericin B. CT scans revealed the presence of a pulmonary infiltrate in the upper left lobe (fig. 3). BAL fluid analysis showed normal percentages of neutrophils (0.9%), and lymphocytes (6%). Microbiological tests on BAL fluid, sputum, blood and urine were negative for pathogens or opportunistic organisms.

Open lung procedure was performed with complete excision of the pulmonary lesion: the biopsy samples showed histological alteration consistent with the diagnosis of BOOP (not shown). The patient recovered completely following surgery.

#### Patient No. 3

Patient No. 3 was treated for APL with four courses of DNR and ARA-C. Six months after diagnosis, because of relapse of APL, one course of rescue therapy was started with DNR, 60  $\text{mg}\cdot\text{m}^{-2}$  *i.v.* on the first day, and ARA-C, 6  $\text{g}\cdot\text{m}^{-2}$  *i.v.* on the first and the second day.

This treatment resulted in severe leucopenia (WBC count  $0.5 \times 10^9$  cells $\cdot\text{L}^{-1}$ ) and, 10 days later, the patient complained of fever and cough. Chest radiographs and CT scans disclosed the presence of multiple nodular lesions in the upper right and left lobes associated with alveolar infiltrates (fig. 4). BAL fluid analysis showed a mild increase in the percentage of neutrophils (2.5%), with normal proportions of lymphocytes (7%), whilst microbiological tests were negative for pathogens or opportunistic organisms.



Fig. 3. – Roentgenographic characteristics of the lung infiltrate in patient No. 2. Chest computed tomography showed the presence of a solitary nodule, without cavitations, in the upper left lobe.



Fig. 4. – Chest computed tomography of the lung infiltrates in patient No. 3, disclosing heterogeneous consolidations in the upper right and left lobes. Multiple nodular lesions, with alveolar and interstitial infiltrates and subpleural consolidations can be observed.

Open lung procedure was performed and demonstrated histological alteration consistent with the diagnosis of BOOP (not shown). The patient recovered completely after surgery.

### Discussion

BOOP is a pathological finding, common in various injuries to the lung, characterized by the presence of granulation tissue within the lumen of distal airspaces [1–4]. This disorder can be idiopathic or can be produced by a variety of immunological-inflammatory processes, including those associated with autoimmune diseases [1, 3, 4], infections [5–7], hypersensitivity reactions [8, 9], myelodysplastic syndromes [12], and treatment with a variety of drugs [14–19] or physical agents [13]. In the three patients described in the present report, the occurrence of BOOP can be related to: 1) remodelling of the distal airways following cytotoxic damage induced by chemotherapeutic agents used to treat the underlying disease; 2) hypersensitive response to the same agents; or 3) healing processes following a localized infection determined by unidentified agent(s).

On the basis of the type and extension of the lung lesions, patients with BOOP may be divided into three groups: 1) Group 1 patients have subacute symptoms, multiple patchy migratory pulmonary involvement of the pneumonia-type, and a good response to corticosteroid therapy; 2) Group 2 includes patients with solitary pulmonary lesions, some with central cavitation, occurring in an acute nonspecific clinical context, and usually undergoing diagnostic surgical excision with complete recovery; 3) Group 3 patients have more insidious onset with progressive dyspnoea, and show diffuse interstitial pulmonary involvement with or without alveolar opacities [22]. The isolated unilateral lesions, seen in Group 2 patients, are also termed "focal organizing pneumonia" or "localized BOOP" [3]. Of the three patients described in the present paper, one patient (No. 2) developed BOOP as a possible "early reaction" to chemotherapy and had the characteristics of Group 2, whilst two other patients (Nos. 1 and 3), who were exposed to multiple treatment and/or to high-dose cytotoxic drugs, had the roentgenographic characteristics of Group 1 (patient No. 1), and of Group 3 (patient No.

3). This observation supports the hypothesis that, in addition to the amount of drug given to the patients, the extent and severity of the pulmonary lesions may be related to an individual genetic predisposition, as suggested for other drug-induced lung diseases [23, 24].

Pulmonary damage due to ARA-C has been reported previously. Although the mechanisms underlying the lung toxicity of ARA-C and anthracyclines are unknown, respiratory distress during the administration of high-dose ARA-C or respiratory symptoms within a month from drug discontinuation are reported as frequent complications in patients with refractory leukaemia [25]. Moreover, treatment with ARA-C has also been associated with an unexplained fatal noncardiac pulmonary oedema, characterized morphologically by intra-alveolar proteinaceous material with minimal parenchymal changes [26]. In contrast, although it is well-recognized that anthracycline is toxic to a variety of human tissues (including myocardium and bone marrow) [27], no direct lung injury has been reported. However, the observation that a polychemotherapeutic regimen, including doxorubicin, induces changes in the composition of pulmonary surfactant in patients with lung cancer, suggests that anthracyclines may contribute to damaging type II pneumocytes [28]. Therefore, although unidentified infectious agents are also possible aetiological factors, a toxic reaction of the two drugs, with involvement of the distal airways, can be hypothesized.

The clinical and roentgenographic characteristics of the pulmonary lesions in the cases described here suggested mycobacterial or mycotic infections. However, all microbiological tests performed on biological fluids (blood, urine, bronchoalveolar lavage) and lung biopsy specimens produced negative results for the presence of pathogenic or opportunistic microorganisms. BOOP has previously been described in patients with refractory anaemia with excess blasts [11] and with chronic myelomonocytic leukaemia [12]. In these two reports, the aetiology of the pulmonary lesions was not identified and a possible subclinical viral infection leading to an immunological-type reaction was suspected [13]. Of course, the possibility of an infectious agent as an aetiological factor, can also be considered in the three patients described here, since no technique is perfect in detecting microorganisms and since BOOP may merely be a sequela of an infectious process, the agent responsible having long since disappeared from the tissue.

Whilst performing bronchoalveolar lavage in these patients, we observed only a mild increase in the proportion of neutrophils in two cases and of lymphocytes in one. In contrast, in previous reports on adult patients with BOOP, a mixed alveolitis was described, with increased proportions of neutrophils, lymphocytes, eosinophils and mast cells [8, 29]. This discrepancy can be, at least partially, explained by differences in: 1) the characteristics of the patient populations evaluated (our three patients had severe leucopenia); and 2) the biological activity of the process, with inflammatory *versus* fibrotic characteristics.

In conclusion, the data presented in this paper suggest that bronchiolitis obliterans organizing pneumonia must be considered in the differential diagnosis of pulmonary infiltrates in patients with leukaemias, treated with anthracyclines and cytosine arabinoside.

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