Noncardiogenic Pulmonary Edema: An Unusual and Serious Complication of Anticancer Therapy

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Key Words. Chemotherapy · Interleukin-2 · Pulmonary toxicity · NCPE · ARDS · Noncardiogenic pulmonary edema · Acute lung injury · Cytarabine · Gemcitabine · All-trans retinoic acid · Arsenic trioxide (As2O3).

ABSTRACT
Noncardiogenic pulmonary edema (NCPE) is a rare and less well-recognizable pulmonotoxic syndrome of anticancer therapy than pneumonitis/fibrosis. NCPE is a clinical syndrome characterized by simultaneous presence of severe hypoxemia, bilateral alveolar infiltrates on chest radiograph, and no evidence of left atrial hypertension/congestive heart failure. The diagnosis of drug-related NCPE relies upon documented exclusion of any infectious, metabolic, or cancer-related causes. The time proximity to therapy with drugs that are known to precipitate NCPE, any preceding episodes of flu-like symptoms during previous chemotherapy courses and possible response to corticosteroids may further support such a diagnosis. Cancer therapeutic agents clearly associated with NCPE are cytarabine, gemcitabine, and interleukin-2, as well as all-trans retinoic acid in acute promyelocytic leukemia patients, while a few other compounds have rarely or occasionally been implicated. The pathophysiology of lung injury in drug-induced NCPE remains unclear. There are indications suggesting that both a direct cytotoxic insult to the lung epithelial cells and induction of a cytokine-triggered inflammatory response may be involved in its pathogenesis. By distinction to drug-induced pulmonary pneumonitis that may lead to permanent pulmonary fibrosis, NCPE if not fatal, can be reversed upon prompt recognition, following immediate discontinuation of the offensive drug and start of intensive supportive treatment and intravenous corticosteroids. The Oncologist 2001;6:153-161

INTRODUCTION
Several cancer therapeutic drugs are known to induce pulmonary damage, which may result in a variety of clinicopathologic syndromes with minor to severe clinical consequences [1]. Clinical syndromes associated with drug-induced pulmonary toxicity include pneumonitis/fibrosis, hypersensitivity lung disease, and noncardiogenic pulmonary edema (NCPE)/acute respiratory distress syndrome (ARDS). These syndromes share a similar symptomatology but differ in regard to the time-relation to cancer treatment, the radiographic findings, the duration of pulmonary damage, and the long-term outcome [2]. Non-specific symptomatology of cough, progressive dyspnea, and often a low-grade fever alert clinicians confronted with the diagnostic challenge to recognize subclinical syndromes and differentiate fully developed drug-induced pulmonary reactions from lung injuries caused by infectious, cardiac, and neoplastic causes.

The most common chemotherapy-associated lung injury is drug-induced pneumonitis. This type of pulmonary toxicity has extensively been studied and attributed to a majority of the pulmonotoxic antineoplastic agents, of which bleomycin is the prototype and nitrosoureas rank second [3-7]. Major concern with this pulmonary toxicity is the potential to progress to irreversible chronic pulmonary fibrosis.

Noncardiogenic pulmonary edema is a rarely cited and less well-recognizable pulmonotoxic syndrome of anticancer therapy. Our recent experience with NCPE that complicated gemcitabine plus docetaxel combination chemotherapy [8] prompted us to investigate existing medical literature in regard to this unusual pulmonary toxicity of anticancer therapy. To our knowledge, this is the first review on anticancer-therapy-associated noncardiogenic pulmonary edema.

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METHODS
A computerized Internet PubMed search of English and non-English language medical literature was conducted by using Reference Manager Version 9.5 (ISI ResearchSoft; PA: http://www.risinc.com/RShome.html) for the period 1965 to 2000, and manually for the period 1960 to 1965. For our search, we used as all-field parameters the generic names of pharmacologic anticancer agents, the words chemotherapy, immunotherapy, and biotherapy, and the key phrases anticancer treatment and drug-induced, combined with the words or key phrases noncardiogenic or primary pulmonary edema, NCPE, pulmonary toxicity, pulmonary disease, respiratory distress syndrome, and acute lung injury.

Reports of drug-induced pulmonary disease related to anticancer treatment had to fit the most accepted definitions for NCPE and ARDS in order to be considered for this review [9-11]. NCPE, also termed as Acute Lung Injury (ALI), is a clinical syndrome characterized by simultaneous presence of severe hypoxemia, bilateral alveolar infiltrates on chest radiograph, and no evidence of left atrial hypertension. The term ARDS is applied to the most severe cases of acute respiratory failure. According to the criteria set by the American-European Consensus Conference on ARDS, a ≤200 mmHg value of quotient PaO\(_2\)/FiO\(_2\) (arterial oxygen-tension/fractional inspired-oxygen) defines ARDS, while ≤300 mmHg characterizes ALI.

ANTICANCER THERAPY-INDUCED NONCARDIOGENIC PULMONARY EDEMA

Clinical Presentation—Diagnosis
NCPE is a rare but major complication of anticancer therapy. This typically presents as a sub-acute clinical syndrome characterized by severe dyspnea, cough, tachypnea, fatigue, and a low-grade fever that occurs shortly after or within a few days following the administration of the offensive pharmaceutical agent or agents [8, 12, 13]. Patients with drug-induced NCPE are usually markedly hypoxemic, with crackles on auscultation and chest radiography showing confluent alveolar consolidations almost identical to those seen in congestive heart failure, and a normal-size heart [14].

Diagnosing drug-induced NCPE is actually an exercise of exclusion, as there is no diagnostic test available. Diagnosis relies upon typical radiograph findings [15] and the documented exclusion of heart dysfunction and any infectious, metabolic, or cancer-related causes. The time proximity to administration of drugs known to precipitate NCPE, any preceding episodes of flu-like symptoms during previous chemotherapy courses, and possible response to corticosteroids may further support such a diagnosis. By distinction from drug-induced pulmonary pneumonitis that potentially may evolve to pulmonary fibrosis, NCPE if not fatal, can be fully reversed upon prompt recognition, following discontinuation of offensive drugs and immediate start of intensive support treatment and intravenous corticosteroids.

Cancer therapeutic agents that clearly precipitate NCPE are cytarabine, gemcitabine, and interleukin 2 (IL-2), and the all-trans retinoic acid and arsenic trioxide (As\(_2\)O\(_3\)) in acute promyelocytic leukemia patients, while a few more compounds have rarely or occasionally been implicated (Table 1).

Biotherapeutic Agents
Among biological agents, recombinant IL-2 (rIL-2) has been clearly associated with the induction of NCPE toxicity, while there is some weak evidence for a similar pulmonotoxic potential of white blood cell growth-stimulating factors.

IL-2, a glycoprotein naturally produced by human T cells during immune response, was introduced in cancer therapeutics 15 years ago as a novel approach to the treatment of solid tumors [16, 17]. This biological response modifier is currently employed in the management of metastatic melanoma and renal cell carcinoma, alone or in combination with chemotherapy or biotherapy [18-21].

Unfortunately, the clinical development of rIL-2 has been compromised by frequently associated toxicities and a narrow therapeutic index [22-24]. Regarding pulmonary toxicity, rIL-2 given intravenously is commonly complicated by NCPE. This occurs in the context of a vascular leak syndrome, the most frequent complication of IL-2, and is mediated via a mechanism of increased microvascular permeability [25, 26]. It is now clear that rIL-2-induced pulmonary toxicity is a dose-related phenomenon that tends to resolve within a few days upon treatment discontinuation [27].

Initial clinical testing identified malaise and weight gain as the dose-limiting toxicities of systemic administration of rIL-2 [28], whereas further clinical experience revealed a significant incidence of NCPE in patients treated with high-dose intravenous rIL-2 [29]. The incidence rate as recorded in the first large cohorts of treated patients ranged from 10%-20%, with a considerable number of treated patients requiring intubation [27, 30, 31]. Interestingly, newest clinical data show a decline in rIL-2-related pulmonary toxicity, obviously due to improvement in key safety issues such as eligibility screening and optimization of therapeutic conditions. Kannmala et al. reviewed safety data of high-dose bolus rIL-2 (720,000 IU/kg every 8 h) administered in 1,241 cancer patients over a 12-year period and found a clear improvement in rIL-2 safety profile with a remarkable drop from 12% to 5% in the incidence of NCPE [32]. The feasibility and the safety of long-term administration of subcutaneous rIL-2 at conventional...
doses of 4.5 million IU/day, three times weekly, has been well established [33] while novel locoregional administration strategies, such as the inhalation of nebulized rIL-2, are being investigated with the aim of improving its therapeutic index [34]. The more favorable toxicity profile of subcutaneous, compared with intravenous, bolus administration of rIL-2, is possibly attributed to a lower systemic absorption (30% of the injected dose) and a better pharmacokinetic profile (sustained systemic exposure and lower peak levels) associated with this route [22].

Hematopoietic growth factors G-CSF and GM-CSF have both been associated as causative or contributing factors with the development of pulmonary toxicity. G-CSF administered during bleomycin-containing chemotherapy regimens may enhance subclinical bleomycin pulmonary toxicity [35, 36], while a possible pulmonotoxic synergy has been suggested for the combination of GM-CSF with chemoradiotherapy in small cell lung cancer patients who received this treatment [37]. Regarding pulmonary edema, G-CSF and GM-CSF have occasionally been implicated with the development of true NCPE, as a small number of published case reports indicate, not all of them well documented [38-40]. It is most possible that the underlying pathophysiological machinery in NCPE cases is the same as with the capillary-leak syndrome that has more commonly been associated with the clinical use of these hematopoietic factors [41-43]. It should be recognized that a definite association of G-CSF and GM-CSF with pulmonary toxicity in

<table>
<thead>
<tr>
<th>Therapy/agent</th>
<th>Reported-estimated incidence</th>
<th>Characteristics/comments</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytarabine (high dose)</td>
<td>high</td>
<td>Potentially fatal toxicity described in leukemia patients treated with moderate to high cytarabine doses (1-1.5 g/m²/continuous infusion, or &gt;3 g/m² as 2 h IV infusion per 12 h) over 3 to 4 days. It develops 1-2 weeks post chemotherapy usually at initial course. Pathophysiology: increased alveolar capillary permeability</td>
<td>[47-49, 104]</td>
</tr>
<tr>
<td>Recombinant IL-2 (high dose intravenous)</td>
<td>3%-20%</td>
<td>Described in renal cancer and melanoma patients, usually in the context of generalized vascular leak syndrome. Severe but reversible on discontinuation of IL-2. An incidence decline is being recorded over the last decade reflecting an improvement in safety keys as the screening of eligible patients and the optimization of therapeutic conditions. Pathophysiology: a damaging effect on vascular endothelial cells by cytokines</td>
<td>[23, 27, 32]</td>
</tr>
<tr>
<td>Bone marrow transplantation</td>
<td>moderate</td>
<td>Bone marrow transplant patients may develop NCPE in the context of systemic capillary leak syndrome 1-2 months following high-dose chemotherapy. A pivotal contribution by circulating leukocytes is suggested.</td>
<td>[75]</td>
</tr>
<tr>
<td>All-trans-retinoic acid (ATRA)</td>
<td>12%</td>
<td>It occurs in the context of ATRA syndrome that may develop in acute promyelocytic leukemia patients undergoing remission induction treatment with ATRA and is characterized by fever, respiratory distress, peripheral edema and pleural or pericardial effusions. Treatment with corticosteroids effective if started early.</td>
<td>[82]</td>
</tr>
<tr>
<td>Arsenic trioxide (As₂O₃)</td>
<td>15%</td>
<td>Same as with ATRA.</td>
<td>[83]</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>0.1%</td>
<td>It is usually building up over a number of courses, but it may also occur after a single administration. Life-threatening but also reversible upon treatment discontinuation and start of intensive supportive therapy and IV corticosteroids.</td>
<td>[54, 56-60]</td>
</tr>
<tr>
<td>Gemcitabine plus docetaxel</td>
<td>rare</td>
<td>In patients with solid tumors. Similar clinical features and outcome as with single gemcitabine.</td>
<td>[8, 66]</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>anecdotal</td>
<td></td>
<td>[68]</td>
</tr>
<tr>
<td>Mitomycin plus vinblastine</td>
<td>2%</td>
<td>It tends to occur shortly after chemotherapy administration.</td>
<td>[69, 71]</td>
</tr>
<tr>
<td>Intrathecal methotrexate</td>
<td>occasional</td>
<td>Three cases have been reported of rapidly developing respiratory distress following the administration of methotrexate into the cerebrospinal fluid.</td>
<td>[73, 74]</td>
</tr>
<tr>
<td>G-CSF</td>
<td>occasional</td>
<td>Reported at a sequential administration regimen.</td>
<td>[38-40]</td>
</tr>
<tr>
<td>Dacarbazine plus fotemustine</td>
<td>anecdotal</td>
<td></td>
<td>[105]</td>
</tr>
</tbody>
</table>

Note: Characterizations high, moderate, rare, occasional, and anecdotal are given in cases of lack of clear incidence data and must be loosely interpreted.
most of the clinical studies is rather poorly documented, but the pulmonotoxic potential of G-CSF has been highlighted in a single preclinical study. Hierholzer et al. have shown that installing G-CSF into the lungs of rats by intratracheal injection resulted in recruitment of neutrophils, lung injury, and impaired pulmonary function [44].

Cytotoxic Drugs

Two cytotoxic antimetabolites, cytarabine, and gemcitabine, both analogues of the nucleoside cytidine, have clearly been associated with the development of pulmonary toxicity of the NCPE type. Cytarabine is used in the chemotherapy of leukemia and lymphoma, and gemcitabine is used in the chemotherapy of solid tumors. These agents compete with deoxyctidine triphosphate for incorporation into the C sites of the growing DNA strand and halt DNA synthesis in progress, inducing cell apoptosis primarily at the S phase [45, 46].

Treatment of leukemia patients with high or moderate doses of cytarabine has been associated with the development of NCPE at a relatively high rate. Andersson et al. reported a 12.5% incidence of fatal pulmonary edema in 103 relapsed leukemia patients at a median time of 16 days from the initiation of high-dose cytarabine therapy. Postmortem findings in seven patients who died of ARDS showed a massive pulmonary edema with a highly proteinaceous intra-alveolar infiltrate, and in one case diffuse alveolar damage. No inflammatory changes were detected [47]. Similar toxicity has also been seen in pediatric patients. Shearer et al. described a fatal pulmonary insufficiency in 5 of 22 pediatric patients treated with high-dose cytarabine and G-CSF support for relapsed acute myelogenous leukemia. Postmortem examination disclosed profound pulmonary edema [48]. In another study, Haupt reviewed clinical and pathologic features of 181 patients with leukemia who had been autopsied at the Johns Hopkins Hospital. They found a highly significant increase in the frequency of pulmonary edema in 51 patients (it was massive in 24 patients) who were treated with cytarabine within the last 30 days prior to their death as compared with non-cytarabine-treated patients. These investigators failed to detect any other cause possibly related to the observed pulmonary edema in 67% of the cases [49]. An interesting syndrome characterized by pulmonary edema, fever, and diarrhea was reported in 4 of 23 lymphoma patients who were treated with high-dose cytarabine. High concentrations of tumor necrosis factor-alpha and platelet activating factor activity were found in the serum of two of those patients [50]. Finally, a review of radiography findings in patients treated with cytarabine who developed pulmonary complications demonstrated diffuse consolidations of the alveolar pattern in both lungs that regressed within 3 to 7 days in the majority of patients who recovered [15].

Gemcitabine is currently employed in the treatment of solid tumors, as a drug of a particularly modest toxicity profile with a low incidence of the side effects normally associated with cytotoxics [51]. In regard to pulmonary toxicity a self-limiting dyspnea has been reported in 5%-8% of patients treated with this agent [52] while true NCPE was recorded in clinical trials at an incidence of about 0.1% [53]. Interestingly, flu-like symptoms and fever have also been reported in 20%-35%, and peripheral edema in up to 20% of the patients treated with gemcitabine [51]. Gemcitabine-induced pulmonary toxicity usually upsurges after a number of repeated drug administrations gradually building up, although occasionally it has also been reported to occur after a single-dose administration [54-56]. A small number of NCPE cases associated with the gemcitabine administration have been reported so far. In the first published report Pavlakis et al. presented three cases of cancer patients who developed NCPE/ARDS while being treated with gemcitabine. Two patients died, after being repeatedly challenged with gemcitabine despite persistent episodes of dyspnea following first chemotherapy courses. Corticosteroids provided maximum benefit in a third patient in whom they were commenced early at diagnosis and were coupled with discontinuation of gemcitabine [54]. Following this report, two fatal and three successful corticosteroid-managed cases were reported [57-60]. In most of these cases a diffuse alveolar damage consistent with acute respiratory distress syndrome was found and systemic corticosteroids seemed to help if started early at diagnosis.

There are also a few other cytotoxic compounds that have occasionally been associated with NCPE. Those are docetaxel, vinblastine and intrathecal methotrexate. Docetaxel, a novel mitotic spindle poison that acts as a microtubule stabilizer, has only infrequently been associated with the development of pulmonary toxicity, that is usually of the type of hypersensitivity pneumonitis not meeting the criteria for NCPE [61, 62]. Notably, a fluid retention syndrome is known to occur in as many as 20%-60% of nonpremedicated patients treated with the agent, but this is typically peripheral, with pleural effusions reported only occasionally [63-65]. Although no NCPE has been attributed to docetaxel as a single agent to date, several cases have been reported with its combination with gemcitabine and radiotherapy [8, 66, 67]. Vinblastine as a single agent has anecdotally been associated with the development of NCPE [68], but this toxicity seems to occur more often when combined with mitomycin [69-71].

Although the most common pulmonary disorder connected with methotrexate is a gradually developing interstitial pneumonitis in rheumatoid arthritis patients [72], three cases of NCPE have been reported that were associated with intrathecal methotrexate. The clinical course, radiology
findings, and in one patient, the pathology report favor the diagnosis of NCPE in these cases [73, 74].

A high incidence of NCPE has been reported to occur in allogeneic and autologous bone marrow transplant patients in a single study. In those patients, NCPE presented in the context of a capillary leak syndrome and was accompanied by generalized organ dysfunction in many cases [75]. It is thought that induction chemotherapy may also play some role in the development of lung toxicity in these patients. Data suggest that standard-dose chemotherapy produces asymptomatic pulmonary dysfunction and inflammation, which may prime the lungs for further injury by high-dose chemotherapy. In a prospective study, high-risk breast cancer patients developed a 12.6% decrease of diffusing capacity of the lungs for carbon monoxide (DLCO) after three cycles of induction chemotherapy with CAF (cyclophosphamide, doxorubicin, 5-fluorouracil) and prior to high-dose chemotherapy with autologous bone marrow or peripheral blood progenitor cell support [76].

ATRA Syndrome

The vitamin A derivative all-trans-retinoic acid (ATRA) and As203 are two drugs with the potential to induce granulocytic differentiation and promote apoptosis of leukemic promyelocytes [77-79]. Currently used in the treatment of acute promyelocytic leukemia [80, 81], these agents have both been associated with the development of NCPE/ARDS in the context of ATRA syndrome. This is a life-threatening complication that occurs in a quarter of patients with acute promyelocytic leukemia who undergo remission induction treatment with ATRA or As203, with or without chemotherapy [82, 83]. The ATRA syndrome characterizes a loosely defined constellation of signs and symptoms that primarily consist of fever and respiratory distress, but also of weight gain, peripheral edema, pleural or pericardial effusions, and hypotension [84]. The pathophysiology of the ATRA syndrome is uncertain, but in vitro data provide evidence that the induction of inflammatory cytokines in acute promyelocytic leukemia cells may play an important role in its pathogenesis [77].

Pathophysiology

The exact mechanism of lung injury in the case of NCPE related to cancer therapeutic agents varies with each class of drugs involved, but overall, it remains poorly defined. It must be emphasized that comorbidities existing in cancer patients potentially complicate the attempt to identify an unequivocal explanation for these clinical findings. Furthermore, in combination chemotherapies or high-dose chemotherapies with G-CSF support, it is quite difficult to mark out the major offensive compound, although lung toxicity can obviously be amplified when pulmonotoxic agents are used concurrently.

Regarding cytotoxic agents, a direct insult by the offensive agent to the alveolar type I pneumocytes or pulmonary vascular endothelial cells and the triggering of a cytokine-mediated inflammatory response appear to be the most frequently involved pathogenic mechanisms. Findings from leukemia patients who died of ARDS following treatment with high-dose cytarabine revealed massive edema and partly diffuse alveolar damage without inflammatory reaction, probably indicating that a direct cytocidal result was a most contributing pathogenetic mechanism in those cases [47]. The hypothesis for the involvement of a cytokine-mediated inflammatory response is suggested by the drug-related fever that occurs in almost half of the patients treated with cytarabine or gemcitabine [85] and the rapid response to corticosteroids reported by several investigators [60, 86].

Additional data provide evidence indicating the involvement of several cytokines, such as tumor necrosis factor-alpha and platelet activating factor in the development of lung injury [50, 87, 88]. Regarding a possible implication of the dosage in the development of NCPE, a dose/pulmonary-toxicity relationship has only been documented for cytarabine, while this does not seem to be the case with gemcitabine [89, 90]. Whatever the exact mechanism of pathogenesis of the lung injury in the case of chemotherapy-induced NCPE, the end-result is an increase in vascular permeability accompanied by extravasation of fluids and proteins into the air space [9]. This has been clearly documented by autopsy findings [47, 54]. Interestingly, two cancer therapeutic agents with pulmonotoxic potential are also known to induce a capillary leak syndrome [51, 91].

The pathogenesis of the lung injury that is related to intravenous administration of high doses of recombinant IL-2 has been investigated extensively. Initial preclinical studies suggested that microvasculature damage, causing a generalized increase of vascular permeability to albumin, was the basic mechanism of rIL-2-induced NCPE [25]. Subsequent studies went into more detail and associated the systemic administration of rIL-2 with lesions of venous and capillary endothelia, alveolar basement membrane, and type I epithelial cells in animals, while leukocyte or platelet activation, generation of free radicals, and activation of the complement system have also been suggested to be involved in its pathogenesis [92-97]. Despite a widening evidence of the involvement of various cytokines released by activated lymphoid cells in the pathogenesis of rIL-2-induced NCPE, the exact mechanism of the damaging events that drive this clinical syndrome remain unclear [23, 33]. Recent demonstration of functional IL-2 receptors on type II pneumocytes indicates that these cells may also
become involved in the pathogenesis of rIL-2-induced NCPE [98].

Regarding NCPE that presents in the context of the ATRA syndrome (see above), activation of production of inflammatory cytokines by acute promyelocytic leukemia cells after exposure to ATRA or As2O3 seems to play an important role in its pathogenesis. In vitro data suggest that acute promyelocytic leukemia cells may produce an increased expression of IL-1 beta, tumor necrosis factor-alpha, IL-8, L-selectin, and intercellular adhesion molecule-1 after induction of differentiation with ATRA, an effect considered related to the progress of the differentiation [77, 99, 100]. The similarity of the clinical phenomena that characterize the ATRA syndrome with those observed after increased production or administration of exogenous cytokines, the overexpression of which has been shown in vitro to be activated after exposure of acute promyelocytic leukemia cells to ATRA, suggests a link between the ATRA syndrome/NCPE and increased production of cytokines and surface integrins during the process of induction of differentiation.

Finally, research on systemic capillary leak syndrome (SCLS) that is a distinct clinical entity characterized by attacks of a marked shift of plasma from the intravascular to the extravascular space may offer an additional theoretical basis for the interpretational approach of the pathophysiology underlying chemotherapy-related NCPE. There is evidence for a complement-mediated injury that leads to a breakdown of the endothelial barrier and plasma leakage in SCLS [101-103].

**Treatment**

Awareness of early recognition of evolving lung toxicity and withdrawal of the possibly offensive drug or drugs are suggested as the most important steps toward successful management of drug-induced NCPE. Intravenous corticosteroids, if started early in the course of drug-induced NCPE, diuretic therapy, and respiratory support with or without mechanical ventilation have reportedly salvaged a number of patients from this pulmonary toxicity.

**CONCLUSION**

It is important for practicing oncologists to realize that a number of cancer-therapeutic agents can produce, or interact with other drugs to produce, noncardiogenic pulmonary edema. Prompt evaluation of any new respiratory symptoms that occur in patients who are treated with pharmaceutical agents potentially inducing NCPE is important for early detection of this severe complication. Patients with pulmonary compromise should be hospitalized and can successfully be managed with high-dose corticosteroids, diuretics, and oxygen supplementation. Immediate discontinuation of chemotherapy is recommended upon suspicion of lung toxicity, and in disputed cases, a lung biopsy should be taken into consideration.

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