which may help with the differential radiologic diagnosis of this entity with respect to other processes with an identical presentation:

1. Patients with mitral valve insufficiency and pulmonary edema localized in the RUL usually present with clinical symptoms of left heart failure. All our patients reported dyspnea and cough.

2. In the presence of a personal history of mitral valve prolapse, atypical localized pulmonary edema in the RUL should be considered as the first possibility and ultrasound examination should be performed routinely.

3. If there is no additional infection, fever or other infectious signs are absent. In fact, none of our patients presented with an increase in body temperature.

4. Since this entity is just another, although atypical, form of left heart failure, the observation of an increase in the cardiac silhouette on radiograph, and especially left atrial enlargement, is not uncommon. All our patients presented with cardiomegaly.

5. For this reason, one expects to find radiologic signs associated with postcapillary pulmonary hypertension (inverted blood flow distribution, pulmonary vascular blurring, central peribronchial cuffing, septal lines, pleural effusion, etc). All of our cases were accompanied by at least one of these additional radiologic findings.

6. In some cases, the special distribution of the edema fluid, in a central disposition, unlike that which one would expect to find in an infectious process, may provide additional diagnostic information.

CONCLUSION

We believe that, in the presence of any process of consolidation of the pulmonary airspace, selectively or predominantly localized in the RUL, with or without associated involvement of the middle lobe, the possibility of localized pulmonary edema secondary to mitral valve insufficiency should be considered, particularly if there are additional clinical or radiologic data of left heart failure.

REFERENCES


Impairment in Gas Exchange After Granulocyte Colony Stimulating Factor (G-CSF) in a Patient With the Adult Respiratory Distress Syndrome*

Gregory J. Schilero, M.D.; John Oropello, M.D., F.C.C.P.; and Ernest Benjamin, M.D., F.C.C.P.

We describe the previously unreported finding of reproducible arterial desaturation after successive injections of granulocyte colony stimulating factor in a orthotopic liver transplant recipient with the adult respiratory distress syndrome and antibiotic-induced neutropenia.

(Chest 1995; 107:276-78)

ANC=absolute neutrophil count; ARDS=adult respiratory distress syndrome; Fio2=fractional inspired oxygen content; G-CSF=granulocyte colony stimulating factor; GM-CSF=granulocyte-macrophage colony stimulating factor; OLT=orthotopic liver transplant;

Colony stimulating factors, namely granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF), are used in a variety of clinical settings where absolute neutropenia complicates otherwise standard chemotherapeutic regimens, and in primary diseases of the bone marrow (ie, myelodysplasia). Their use is less well described in antibiotic-induced neutropenia, a finding often seen in critically ill patients. Besides inducing neutrophil proliferation, both G-CSF and GM-CSF stimulate neutrophil activation. The development of adult respiratory distress syndrome (ARDS) in patients treated with GM-CSF has been reported. To our knowledge, this is the first report of a deterioration in pulmonary function due to G-CSF administration in a neutropenic patient with ARDS.

CASE REPORT

A 28-year-old woman with necrotizing hepatitis B infection, cirrhosis, and renal failure requiring hemodialysis, underwent orthotopic liver transplant (OLT). Immunosuppressive therapy with steroids and cyclosporine was instituted. The postoperative course was complicated by anorectomy for upper gastrointestinal bleeding (postoperative day [POD] 6), peritonitis with Enterococcus faecium and Candida albicans (POD 15), and an anastomotic biliary leak repaired with exteriorization of the common bile duct (POD 21). Ampicillin-sulbactam, gentamicin, and amphotericin B were used to treat peritonitis. On the 27th day post-OLT, the patient developed fever and respiratory distress. An alternative antibiotic regimen of imipenem-cilastatin and vancomycin was used successfully to treat a lebar pneumonia. A liver biopsy specimen demonstrated no evidence of rejection. Seven weeks after liver transplantation, a cholechochoejunostomy was performed for reinsertion of the common bile duct. Two days

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276 Gas Exchange Impairment After G-GSF in a Patient With ARDS (Schilero, Oropello, Benjamin)
later, the patient was emergently intubated for impending respiratory failure. With 100 percent oxygen and positive end-expiratory pressure 10 cm H2O, the PaO2 was 80 mm Hg. A chest radiograph revealed bilateral pulmonary infiltrates. Pulmonary catheter measurements were consistent with ARDS ( wedge pressure=12 mm Hg). The cardiac output was 4.7 L/min. Empiric intravenous trimethoprim-sulfamethoxazole and ganciclovir therapy was instituted to treat possible Pneumocystis carinii pneumonia or cytomegalovirus infection. Baseline hematologic parameters included a white blood cell (WBC) count of 11.1X109/L, an absolute neutrophil count (ANC) of 7.1X109/L, and a hemoglobin concentration of 10.6 g/dl. Bronchoalveolar lavage findings were nondiagnostic. The next 7 days, the pulmonary infiltrates progressed despite therapy. After 13 days of receiving ganciclovir and trimethoprim-sulfamethoxazole, the WBC count fell to 1,500X109/L, and the ANC to 690X109/L.

A decision was made to administer G-CSF in a dosage of 5 µg/kg/d subcutaneously. Arterial desaturation requiring 100 percent oxygen was noted within several hours of G-CSF administration on 2 consecutive days requiring its discontinuation (Table 1). Nine weeks following liver transplantation, and 16 days after developing ARDS, an open lung biopsy was remarkable for diffuse alveolar damage consistent with the proliferative phase of ARDS. No pathogenic organisms were found. The patient subsequently made a slow recovery and was eventually extubated several weeks later.

**Discussion**

Granulocyte colony stimulating factor and GM-CSF have been approved for use in neutropenic states following myelotoxic chemotherapy for nonmyeloid tumors (G-CSF), and following autologous bone marrow transplantation for lymphoid tumors (GM-CSF).1 Their use has also been described in congenital neutropenic states, the myelodysplastic syndrome, aplastic anemia, and in AIDS-related neutropenia.2,3 Beneficial reductions in the period of neutropenia, rates of infection incidence, and length of hospitalization have been variably noted.2,7

Both G-CSF and GM-CSF are endogenous glycoproteins involved in the proliferation and maturation of neutrophils and, in the case of GM-CSF, monocytes and eosinophils as well. Granulocyte-macrophage CSF exhibits numerous direct and indirect effects on neutrophil function. These include enhanced survival, increased synthesis of platelet-activating factor, upregulation of genes encoding for interleukin 1 and interleukin 6, increased arachidonate metabolism and synthesis of 5-lipoxigenase products, enhanced phagocytic and bactericidal function, altered expression of cell surface receptors, inhibition of random migration, and the generation of oxygen-derived free radicals.4,5 Enhanced monocyte function including increased cytotoxicity and elaboration of tumor necrosis factor-alpha have also been described.4 Not surprisingly, GM-CSF administration is associated with various side effects, including myalgia, arthralgia, flushing, anorexia, and generalized skin eruptions. Occasionally, a syndrome characterized by nausea, vomiting, tachycardia, hypotension, musculoskeletal pain, dyspnea, and arterial oxygen desaturation is observed approximately 3 h after initial GM-CSF administration.5 The observed hemodynamic compromise and hypoxemia are hypothetically related to enhanced effector cell function with the release of inflammatory mediators. The G-CSF, on the other hand, has a narrower spectrum of activity more limited to neutrophil proliferation, although it shares with GM-CSF some stimulatory effects on neutrophil function: prolonged survival, upregulation of cellular adhesion molecules, and enhanced superoxide production.5 Granulocyte CSF administration is correspondingly well tolerated, the most common side effect being bone pain and occasionally rash.1,4

### Table 1—Changes in the ANC and Gas Exchange in Response to G-CSF Administration*

<table>
<thead>
<tr>
<th>Time</th>
<th>HR</th>
<th>MAP, mm Hg</th>
<th>CO, L/min</th>
<th>SV, ml/beat</th>
<th>PAOP</th>
<th>PaO2, mm Hg</th>
<th>PaCO2, mm Hg</th>
<th>Flo2, l</th>
<th>Alveolar-Arterial Gradient</th>
<th>Qs/Qt, §</th>
<th>RR, Vent</th>
<th>ANC, X109/L</th>
<th>Hb, g/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>117</td>
<td>89</td>
<td>7.1</td>
<td>61</td>
<td>12</td>
<td>62</td>
<td>38</td>
<td>60</td>
<td>28</td>
<td>20</td>
<td>20</td>
<td>11</td>
<td>11</td>
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<tr>
<td>Day 1</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pre-GCSF</td>
<td>105</td>
<td>94</td>
<td>7.7</td>
<td>73</td>
<td>14</td>
<td>67</td>
<td>36</td>
<td>60</td>
<td>316</td>
<td>20</td>
<td>600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 h post-GCS</td>
<td>58</td>
<td>51</td>
<td>7.0</td>
<td>73</td>
<td>20</td>
<td>97</td>
<td>42</td>
<td>100</td>
<td>563</td>
<td>41</td>
<td>26</td>
<td>10.5</td>
<td></td>
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<tr>
<td>Day 2</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-GCSF</td>
<td>82</td>
<td>96</td>
<td>4.9</td>
<td>77</td>
<td>6</td>
<td>47</td>
<td>29</td>
<td>60</td>
<td>305</td>
<td>27</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>5 h post-GCS</td>
<td>158</td>
<td>33</td>
<td>514</td>
<td>8</td>
<td>100</td>
<td>33</td>
<td>100</td>
<td>100</td>
<td>43</td>
<td>26</td>
<td>10</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>8 h post-GCS</td>
<td>100</td>
<td>33</td>
<td>100</td>
<td>100</td>
<td>569</td>
<td>33</td>
<td>100</td>
<td>100</td>
<td>43</td>
<td>26</td>
<td>10</td>
<td>10.2</td>
<td></td>
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<tr>
<td>Day 3</td>
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<td></td>
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<td></td>
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<tr>
<td>(No G-CSF)</td>
<td>73</td>
<td>37</td>
<td>380</td>
<td>9</td>
<td>56</td>
<td>37</td>
<td>70</td>
<td>399</td>
<td>30</td>
<td>26</td>
<td>2,78</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>05:10</td>
<td>105</td>
<td>99</td>
<td>56</td>
<td>53</td>
<td>16</td>
<td>14:11</td>
<td>56</td>
<td>35</td>
<td>30</td>
<td>26</td>
<td>11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*HR=heart rate; MAP=mean arterial pressure; CO=cardiac output; SV=stroke volume; PAOP=pulmonary artery occlusion pressure; Qs/Qt=venous admixture (shunt fraction); G-CSF dose=5 µg/kg/d subcutaneously.
†Ventilator mode (assist control) and settings: tidal volume (600 ml) and PEEP (4 cm H2O) remained constant throughout the 4-day period. Changes in ventilator rate are noted (RR vent).
§The A-a gradient was calculated using the alveolar gas equation.
¶The venous admixture/shunt fraction was calculated from the mixed venous blood gases and the shunt equation: CaO2-CaO2/CaO2-CvO2X100.
||Hemoglobin saturations were determined by CO-oximetry.
¶ Represents shunt fraction on Flo2 100 percent.
Few studies have reported the effects of colony stimulating factors on the development of ARDS. Verhoef and Boogaerts\(^6\) describe the development of diffuse lung injury consistent with ARDS in a patient with neutropenia with the myelodysplastic syndrome by the 12th day of subcutaneously administered GM-CSF and cytosine arabinoside. Neutrophils from this patient were found to express increased CD11b and CD18 surface glycoproteins associated with increased cellular adhesion to endothelium, decreased chemotaxis, and increased superoxide generation. These processes were implicated in the resultant lung injury.

In a study using G-CSF, Heyll, et al\(^8\) found that subcutaneous administration to a patient who developed pancytopenia and ARDS during induction chemotherapy for acute lymphoblastic leukemia resulted in a prompt recovery in the peripheral neutrophil count, improved pulmonary function, and ultimately resolution of ARDS. They proposed that neutropenic patients with acute leukemia undergoing chemotherapy are most commonly found to have an underlying streptococcal infection, and the subsequent rise in neutrophil count in response to G-CSF therapy in this subpopulation may be beneficial to augment host defenses.

Herein, we describe the case of a liver transplant recipient with ARDS and absolute neutropenia (<700X10\(^6\)/L) who, after subcutaneous administration of G-CSF, had apparent arterial desaturation within 4 to 6 h on 2 consecutive days. As outlined in Table 1, the ANC rose from 690X10\(^6\)/L to 1,370X10\(^6\)/L within 24 h after the first dose of G-CSF, and increased to 2,790X10\(^6\)/L following the second dose (between days 2 and 3). Worsening gas exchange was noted within 6 to 8 h of G-CSF administration (5 µg/kg, subcutaneously at 10 AM) on 2 consecutive days, ultimately requiring 100 percent oxygen to maintain the hemoglobin saturation above 90 percent. The alveolararterial gradient increased from a baseline of 310 to 330 mm Hg to greater than 560 mm Hg corresponding to an increase in the venous admixture from approximately 27 percent to greater than 40 percent. Gas exchange subsequently improved, and the FIO\(_2\) was reduced to baseline values within 24 h. No significant hemodynamic or temperature fluctuations were noted following administration of G-CSF.

To our knowledge, this is the first case report implicating the use of G-CSF with worsening hypoxemia in a patient with established ARDS. Although a direct relationship between this patient’s arterial desaturation and G-CSF administration is impossible to prove, the temporal relationship between G-CSF infusion and the fall in arterial saturation suggests an association. Granulocyte CSF may, in certain disease states like ARDS, accelerate an already preexisting state of neutrophil activation. Numerous inflammatory mediators have been linked to the pathogenesis of ARDS, including neutrophil activation. The further induction of the inflammatory cascade in response to G-CSF administration could lead to the worsening gas exchange that was seen in our patient.

We conclude that the use of G-CSF in neutropenic patients with ARDS should be undertaken with caution until its effects in this setting are better characterized.

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**REFERENCES**


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**Single Lung Transplantation for Pulmonary Lymphangiomyomatosis**

**Unexpected Need for Extracorporeal Circulation**

Alain Brusset, MD; Pierre Bonnete, MD; Ziadh Hatahet, MD; Philippe Loirat, MD; Alain Bisson, MD; and Marc Fischler, MD

The present case describes an acute respiratory-related hemodynamic failure during a single left lung transplantation in a 32-year-old woman suffering from end-stage pulmonary lymphangiomyomatosis. During the first 5 min of single right lung ventilation, a progressive increase in airway pressure and decrease in tidal volume associated with a decrease in arterial pressure and SpO\(_2\) occurred that were successfully countered by ventilation of the left lung. Proper positioning of the double-lumen tube was confirmed with a fiberoptic bronchoscope. Despite deliberate hypoventilation, within a few respiratory cycles, each further attempt at single lung ventilation was followed by abrupt hypotension, increase in pulmonary artery pressure, while airway pressure rose and tidal volume collapsed. The surgical team saw no signs of right pneumothorax. In these cir-

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*From the Department of Anesthesiology (Drs. Brusset, Hatahet, and Fischler); Intensive Care Unit (Dr. Loirat); and the Department of Thoracic Surgery (Drs. Bonnette and Bisson), Hôpital Foch, Université Paris Ouest, France.*