Nephrotic syndrome in acute promyelocytic leukemia

Borhan Moradveisi
, Kurdistan University of Medical Sciences and Health Services
Armin Rashidi
Washington University School of Medicine in St. Louis
Samin Alavi
Shahid Beheshti University of Medical Sciences
Alireza Eskandarifar
Kurdistan University of Medical Sciences and Health Services

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs
Please let us know how this document benefits you.

Recommended Citation
https://digitalcommons.wustl.edu/open_access_pubs/8410

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact vanam@wustl.edu.
Nephrotic syndrome in acute promyelocytic leukemia

A five-year-old boy presented (Day 0) with gingival bleeding and pancytopenia (white blood cells: 1.7 × 10⁹/L; hemoglobin: 7.3 g/dL; platelets: 16 × 10⁹/L). A coagulation panel was unremarkable. Peripheral blood smear revealed dysmorphic promyelocytes with red-blue granules, folded reniform nuclei and no Auer rods. Bone marrow examination showed immature myeloid cells (>60% promyelocytes) that were positive for myeloperoxidase (MPO), CD117, CD13 and CD33, and negative for CD34 and HLA-DR. Cytogenetic analysis showed a male karyotype with 46,XY, t(15;17)(q24;q21). Quantitative real-time polymerase chain reaction was positive for PML-RARα. A diagnosis of acute promyelocytic leukemia (APL) was established. Induction chemotherapy with daunorubicin (50 mg/m² of acute promyelocytic leukemia (APL) was established. A diagnosis of acute promyelocytic leukemia (APL) was established. Induction chemotherapy with daunorubicin (50 mg/m² Days 1, 3 and 5), cytarabine (100 mg/m² every 12 h, Days 1–10) and thioguanine (100 mg/m² every 12 h, Days 1–10) along with all-trans retinoic acid (ATRA; 45 mg/m² per day in two divided doses starting on Day 1) was initiated on admission Day 2. Prophylactic dexamethasone (0.1 mg/kg twice daily) was administered along with ATRA. On Day 9, the patient developed a hypertensive crisis, bilateral lower extremity edema, proteinuria (24-h urine protein 1000 mg) and hyperlipidemia (triglycerides: 525 mg/dL, total cholesterol: 275 mg/dL). His serum albumin at this time was 3.2 g/dL. Given the above presentation and the definition of nephrotic-range proteinuria in children (>40 mg/m²/h), a diagnosis of nephrotic syndrome (NS) (most likely minimal change disease) was established and steroids (prednisone 2 mg/kg/day) were initiated. Proteinuria and other manifestations of NS resolved on admission Day 26, after which steroids were quickly tapered and eventually discontinued. The patient has now completed the second course of DAT without signs or symptoms of NS. During the second course, he only received prophylactic doses of steroids.

The association of NS with acute myeloid leukemia (AML) is rare, with only 10 cases reported previously (Table 1). There was a remarkable male predominance (80%), and the median age at diagnosis was 33 (range: 3–81) years. Surprisingly, 45% of all cases and all three pediatric cases were APL. NS was present before treatment in 45% of cases, suggesting a direct pathogenic role of leukemia. In other cases, anthracycline therapy was the main culprit. Histopathological findings on renal biopsy did not reveal a unique pattern and varied from minimal change disease (MCD) to focal segmental glomerulosclerosis (FSGS), immune complex deposition, macrophage infiltration, membranous glomerulonephritis, proliferative glomerulonephritis and detachment of epithelial cells from the glomerular basement membrane. From the nine patients who received some form of treatment for NS, steroids were the chosen treatment in seven patients, with a response rate of 86%; the other two patients were treated only with chemotherapy and NS responded to treatment in both.

A number of mechanisms may explain the rare association between NS and AML. Disruption of podocyte integrity

Table 1. Summary of previous reports on the association between AML and NS

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Age, sex, FAB</th>
<th>Induction regimen</th>
<th>Proteinuria before AML treatment</th>
<th>Possible etiology</th>
<th>Renal histology</th>
<th>Tx of NS, response</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[10], 1972</td>
<td>20, M, n/a</td>
<td>None</td>
<td>+</td>
<td>AML</td>
<td>Membranous GN</td>
<td>None</td>
<td>Death at 6 days (renal failure) CR, relapse at 2 m and death</td>
</tr>
<tr>
<td>[9], 1983</td>
<td>57, M, M4</td>
<td>Vincristine and prednisone, followed by cytarabine, daunorubicin, thioguanine, and prednisone</td>
<td>+</td>
<td>AML</td>
<td>FSGS, immune complex deposits</td>
<td>Steroids</td>
<td>CR, sepsis</td>
</tr>
<tr>
<td>[11], 1986</td>
<td>81, F, M3</td>
<td>Cytarabine, daunorubicin</td>
<td>+</td>
<td>n/a</td>
<td>Proliferative GN</td>
<td>Steroids</td>
<td>CR, sepsis</td>
</tr>
<tr>
<td>[12], 1989</td>
<td>33, M, M2</td>
<td>Cytarabine, daunorubicin</td>
<td>–</td>
<td>Anthracycline</td>
<td>MCD, IgM deposits</td>
<td>Steroids</td>
<td>CR</td>
</tr>
<tr>
<td>[13], 1995</td>
<td>33, F, M3</td>
<td>Cytarabine, daunorubicin, 6-MP, prednisone</td>
<td>–</td>
<td>Anthracycline</td>
<td>Epithelial-GBM detachment</td>
<td>Steroids</td>
<td>CR</td>
</tr>
<tr>
<td>[14], 1996</td>
<td>59, M, M2</td>
<td>Etoposide, cytarabine, daunorubicin</td>
<td>+</td>
<td>M-CSF</td>
<td>Macrophage infiltration</td>
<td>Steroids</td>
<td>CR</td>
</tr>
<tr>
<td>[2], 2002</td>
<td>44, F, M5</td>
<td>Etoposide, cytarabine, daunorubicin</td>
<td>+</td>
<td>AML</td>
<td>n/a, possible MCD</td>
<td>ChemoTx</td>
<td>CR</td>
</tr>
<tr>
<td>[15], 2004</td>
<td>53, M, n/a</td>
<td>Cytarabine, daunorubicin</td>
<td>+</td>
<td>AML</td>
<td>Membranous GN</td>
<td>Steroids</td>
<td>CR</td>
</tr>
<tr>
<td>[16], 2010</td>
<td>9, M, M3</td>
<td>Cytarabine, idarubicin, etoposide, ATRA</td>
<td>–</td>
<td>Anthracycline</td>
<td>FSGS</td>
<td>Steroids</td>
<td>CR</td>
</tr>
<tr>
<td>[1], 2012</td>
<td>3, M, M3</td>
<td>Cytarabine, daunorubicin, ATRA</td>
<td>–</td>
<td>ATRA syndrome</td>
<td>Membranous GN</td>
<td>Steroids</td>
<td>CR</td>
</tr>
<tr>
<td>Our case</td>
<td>5, M, M3</td>
<td>Cytarabine, daunorubicin, thioguanine, ATRA, and dexamethasone</td>
<td>–</td>
<td>Anthracycline</td>
<td>n/a</td>
<td>Steroids</td>
<td>CR</td>
</tr>
</tbody>
</table>

6MP, 6-mercaptopurine; AML, acute myeloid leukemia; ATRA, all-trans retinoic acid; ChemoTx, chemotherapy; CR, complete remission; DAH, diffuse alveolar hemorrhage; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GN, glomerulonephritis; M-CSF, macrophage colony-stimulating factor; MCD, minimal change disease; n/a, not available; NS, nephrotic syndrome; Tx, treatment.

© The Author 2014. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved. For permissions, please email: journals.permissions@oup.com.
and function due to cytokine release has been proposed as a mechanism of nephrotic syndrome during ATRA-induced differentiation syndrome in APL [1]. A causal relationship between NS and AML is further supported by the response of proteinuria to chemotherapy for AML and the association between higher leukemia burden and more proteinuria [1, 2]. Anthracyclines have been proposed as a culprit in the development of NS following treatment of AML since they can cause acute renal tubulointerstitial toxicity [3, 4]. Also, adriamycin rapidly increases the expression of the ligands on podocytes for advanced glycation end products, leading to podocyte stress and glomerulosclerosis in mouse models [5]. Adriamycin is now often used to induce experimental FSGS [6, 7]. Finally, NS in AML may reflect a local immune complex-mediated process [8, 9]. Given the absence of proteinuria before AML treatment in our patient, we believe daunorubicin was the most likely cause of NS in the present case. However, a direct effect of ATRA (e.g. terminal differentiation of promyelocytes and toxic effects of the released granules) cannot be ruled out. He had no signs of recurrent NS after re-exposure to chemotherapy, suggesting re-challenge may be safe in drug-induced NS.

Conflict of interest statement. None declared.

References


Received for publication: 14.4.14; Accepted in revised form: 28.5.14

do: 10.1093/ckj/sfu062

Correspondence and offprint requests to: Armin Rashidi; E-mail: arashidi@dom.wustl.edu

1Department of Pediatric Hematology and Oncology, Besat Hospital, Kurdistan University of Medical Sciences and Health Services, Sanandaj, Iran

2Division of Oncology, Washington University School of Medicine, St. Louis, MO, US

3Pediatric Congenital Hematologic Disorders Research Center, Shahid Beheshi University of Medical Sciences, Tehran, Iran

4Department of Pediatric Nephrology, Besat Hospital, Kurdistan University of Medical Sciences and Health Services, Sanandaj, Iran


B. Moradveisi

Armin Rashidi

Samin Alavi

Alireza Eskandarifar

Downloaded from https://academic.oup.com/ckj/article-abstract/7/4/484/777852 by Washington University, Law School Library user on 16 November 2019