

## From the Clinic

### Nephrotic syndrome in acute promyelocytic leukemia

A five-year-old boy presented (Day 0) with gingival bleeding and pancytopenia (white blood cells:  $1.7 \times 10^9/L$ ; hemoglobin: 7.3 g/dL; platelets:  $16 \times 10^9/L$ ). 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-RAR $\alpha$ . A diagnosis of acute promyelocytic leukemia (APL) was established. Induction chemotherapy with daunorubicin (50 mg/m<sup>2</sup> Days 1, 3 and 5), cytarabine (100 mg/m<sup>2</sup> every 12 h, Days 1–10) and thioguanine (100 mg/m<sup>2</sup> every 12 h, Days 1–10) along with all-*trans* retinoic acid (ATRA; 45 mg/m<sup>2</sup> 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/m<sup>2</sup>/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

Reference, year	Age, sex, FAB	Induction regimen	Proteinuria before AML treatment	Possible etiology	Renal histology	Tx of NS, response	Outcome
[10], 1972	20, M, n/a	None	+	AML	Membranous GN	None	Death at 6 days (renal failure)
[9], 1983	57, M, M4	Vincristine and prednisone, followed by cytarabine, daunorubicin, thioguanine, and prednisone	+	AML	FSGS, immune complex deposits	Steroids +	CR, relapse at 2 m and death
[11], 1986	81, F, M3	None	+	n/a	Proliferative GN	Steroids -	Early death
[12], 1989	33, M, M2	Cytarabine, daunorubicin	-	Anthracycline	MCD, IgM deposits	Steroids +	Death at 26 days (sepsis)
[13], 1995	33, F, M3	Cytarabine, daunorubicin, 6-MP, prednisone	-	Anthracycline	Epithelial-GBM detachment	None	Death at 16 days (DAH)
[14], 1996	59, M, M2	Enocitabine, daunorubicin, 6-MP, cytarabine, vincristine, prednisolone, M-CSF	+	M-CSF	Macrophage infiltration	Steroids +	Death at 14 months (sepsis)
[2], 2002	44, F, M5	Etoposide, cytarabine, daunorubicin	+	AML	n/a, possible MCD	ChemoTx +	Death at 6 months (DAH)
[15], 2004	53, M, n/a	Cytarabine, daunorubicin	+	AML	Membranous GN	Steroids +	n/a
[16], 2010	9, M, M3	Cytarabine, idarubicin, etoposide, ATRA	-	Anthracycline	FSGS	Steroids +	CR at 2 years
[1], 2012	3, M, M3	Cytarabine, daunorubicin, ATRA	-	ATRA syndrome	n/a	ChemoTx +	CR
Our case	5, M, M3	Cytarabine, daunorubicin, thioguanine, ATRA, and dexamethasone	-	Anthracycline	n/a	Steroids +	CR

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.

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.

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