Renal involvement in acute lymphoblastic leukemia (ALL) occurs due to several factors including leukemic infiltration of the kidneys, therapy-related side effects such as tumor lysis syndrome, nephrotoxic drugs, and septicemias. A 3-year-old boy with nephrotic syndrome (NS) who was previously treated with prednisolone and cyclosporine A for 14 months after the initial diagnosis of NS, presented to the emergency department with fever, breathing difficulty, generalized edema, and body pain with pallor, without evidence of lymphadenopathy, hepatosplenomegaly, petechiae, or purpura. On investigation, peripheral blood smear showed blast cells >80% and bone marrow aspiration showed complete replacement of the marrow with L1 lymphoblasts, consistent with a diagnosis of ALL. The exact mechanism of developing acute leukemia after cytotoxic treatment has not been established; the possibility must be considered that the incidence of this malignant disease is increased after cytotoxic treatment for nonmalignant diseases.

Key words: Acute leukemia, Alkylating agents, Antimetabolites, cytotoxic drugs, Immunosuppression, Nephrotic syndrome

ABSTRACT

Renal involvement in acute lymphoblastic leukemia (ALL) occurs due to several factors including leukemic infiltration of the kidneys, therapy-related side effects such as tumor lysis syndrome, nephrotoxic drugs, and septicemias. A 3-year-old boy with nephrotic syndrome (NS) who was previously treated with prednisolone and cyclosporine A for 14 months after the initial diagnosis of NS, presented to the emergency department with fever, breathing difficulty, generalized edema, and body pain with pallor, without evidence of lymphadenopathy, hepatosplenomegaly, petechiae, or purpura. On investigation, peripheral blood smear showed blast cells >80% and bone marrow aspiration showed complete replacement of the marrow with L1 lymphoblasts, consistent with a diagnosis of ALL. The exact mechanism of developing acute leukemia after cytotoxic treatment has not been established; the possibility must be considered that the incidence of this malignant disease is increased after cytotoxic treatment for nonmalignant diseases.

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CASE REPORT

A 3-year-old boy presented with periorbital edema of 10 days duration. His physical examination showed: Weight 20.8 kg (> +3SD), height 96.8 cm (+1SD to +2SD), and blood pressure of 96/50 mmHg. There were no lymphadenopathy, hepatosplenomegaly, bruising, or petechiae. Urinalysis showed 4+ (>1000 mg/dl) proteinuria - whereas serum analysis only showed low total serum protein (41 g/l; normal=60–85 g/l) and low albumin (14 g/l; normal=35–55 g/l) levels. Complete blood count (CBC) was within the normal limits without any abnormal cells on the peripheral blood smear. On the basis of clinical presentation and investigation findings, the diagnosis of NS was made.

Treatment of NS was commenced with daily prednisone (2 mg/kg/day). Following 6 weeks of daily prednisone therapy, nephrotic range proteinuria and clinical symptoms of edema persisted, and a percutaneous renal biopsy was performed at 8th week. A total of 30 glomeruli were available for the examination by light microscopy; 14 of these were demonstrated segmental glomerulosclerosis of varying degree; three glomeruli had global sclerosis. The glomeruli with segmental sclerosis were dispersed throughout the core of the biopsy specimen [Fig. 2]. A mild degree of interstitial fibrosis and tubular dropout (a process that leads to progressive glomerular loss of activated tubular cells which produce cytokines, support inflammatory responses, and dedifferentiate results in nephron loss), along with mononuclear cell infiltrate, were noted. No evidence of neoplastic infiltration by malignant cells was noted.

At the 10th week, the patient had cushingoid features with pretibial and periorbital edema; urinalysis showed proteinuria of 3+ (>300 mg/dl) and serum albumin of 21 g/l. CBC showed WBC 12.1×10^9/l, hematocrit 44.2%, and platelet count 350×10^9/l. A trial with cyclosporin was initiated due to the lack of response to prednisone with the starting dose of 5 mg/kg/day. Prednisone was continued in a tapering dose, and the patient received enalapril and furosemide as adjunctive therapies. 1 month after starting cyclosporine, the baby no longer had edema, and the spot urinary
protein/creatinine ratio was <2 with serum total protein of 70 g/l, and albumin of 38 g/l.

14 months after the initial diagnosis of NS, the patient was presented to the emergency department with fever, difficulty in breathing, generalized edema, and body pain [Fig.1]. Clinical examination showed pallor without lymphadenopathy, hepatosplenomegaly, petechiae, or purpura. CBC showed WBC 175×10^9/l (normal=3.5–12.0×10^9/L), hemoglobin 23 g/l (normal=107–134 g/l), and a platelet count of 20×10^9/l (normal=150–400×10^9/L). Other significant laboratory studies included blood urea nitrogen 52.8 mmol/l (normal=8.0–16.4 mmol/l) and creatinine 141 μmol/l (normal=50–110 μmol/l). Peripheral smear showed blast cells >80%; [Fig. 3] a bone marrow aspiration showed complete replacement of the marrow with L1 lymphoblasts, consistent with a diagnosis of ALL [Fig. 4]. The patient demised from septicemia and multiorgan failure.

**DISCUSSION**

The malignancies, commonly associated with NS, include Hodgkin and non-Hodgkin lymphomas, chronic lymphocytic leukemia, and acute myelogenous leukemia [5]. In the pediatric population, scanty number of cases of ALL has been reported in association with NS. The main line of management in neoplastic and non-neoplastic disorders includes cytotoxic immunosuppressive agents, which plays an important role in the treatment of these disorders.

Alkylating agents, such as cyclophosphamide and chlorambucil, are known to induce secondary malignancies, in particular, leukemia [11]. In some reported cases, cyclosporine has been associated with an increased risk of malignancies [12-14]. Malignancy as a complication of NS, even following treatment with cytotoxic drugs, is uncommon. Berns et al. [14] did not vreport any cases of malignancy on follow-up of 20 such patients. A review of the database, available at Medline/PubMed from 1970 to 2017 showed that NS preceding the diagnosis of ALL has been reported in only five pediatric patients. Among all the reported cases, the time span between the onset of NS and diagnosis of
ALL was under 1 year, except the one patient in which ALL was diagnosed after the 7 years of the initial diagnosis of NS [7-10].

The main pathogenesis of ALL in children with NS has not been determined. There may be three possibilities in support of it; first, the children with NS may have a pre-existing leukemic state, which was masked by prednisone therapy. It is conceivable that abnormal cells were present in the bone marrow but were below the established level necessary for the diagnosis of ALL. The leukemia could have partially treated by prednisone therapy, thus delaying the final diagnosis. Total replacement of the bone marrow occurred within 8–12 weeks as the doubling time of pre-B leukemic cells would have required approximately 24 h [15], and overt leukemia was diagnosed in all but one patient after more than 4 months from the diagnosis of NS. The second possibility, when there was disruption of normal immune surveillance caused by immunosuppressive agents could allow an abnormal clone to go undetected and proliferate. Outgrowth of abnormal cells has been indicated as a crucial factor in the progression of malignancies [16].

Last possibility was that an underlying defect in T-cell function or T-/B- cell cooperation could account for both NS and the risk of malignancies in later life. Shalhoub [17] suggested that NS is a disorder of lymphocyte function and Fiser et al. [18] have demonstrated abnormal T-lymphocyte subsets in children with NS. FSGS has been reported as the main pathology in patients who develop ALL with pre-existing NS [5]. There was no clinical benefit of corticosteroid therapy in such patients [6-9].

CONCLUSION

The treatment of childhood NS with cytotoxic drugs and calcineurin inhibitors is well accepted. The risk of malignancy with such therapy has been generally considered to be low. However, the presence of persistent abnormalities in the hematological profile of nephrotic patients undergoing immunosuppressive therapy needs closer evaluation for underlying leukemia. A lower threshold for bone marrow aspiration in such patients should be considered for early detection and treatment of leukemia.

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