INTRODUCTION
The autoimmune lymphoproliferative syndrome (ALPS) also known as Canale-Smith syndrome is a chronic, non-malignant lymphoproliferative disorder caused by somatic or germ line mutations in the FAS gene which is responsible for programmed cell death (apoptosis).\(^1\) The impaired lymphocyte apoptosis causes accumulation of T-lymphocytes, which are double negative T-cells expressing CD3 and α/β antigen receptors but do not have CD4 or CD8 co-receptors (CD3 + T-cell receptor α/β* CD4-, CD8 -).\(^1\) These T-cells respond poorly to antigens and mitogens and do not produce growth or survival factor (interleukin 2). This defect underlies the clinical manifestations of lymphoproliferation, immune dysregulation and autoimmunity. The lymphadenopathy regresses with age whereas the autoimmunity is characterized by frequent exacerbation and recurrences. The defect can affect any organ system and there is a higher incidence of malignancy.

The authors hereby describe two cases of ALPS with onset in neonatal period.

CASE REPORT

Case 1: A baby girl was born with uneventful spontaneous vaginal delivery (SVD) at term to related parents. She was breast fed and the first doses of polio and tuberculous vaccines were given. On the 20th day of life, she developed mild cough, low grade fever and difficulty in breathing which was progressive. On the 24th day of life, she was admitted in FMH with severe respiratory distress and threw multiple fits, which were generalized tonic clonic type, with cyanosis. She became apneic and was intubated and shifted to ICU.

On examination, she was febrile, tachypnoeic, tachycardic and had severe respiratory distress. On auscultation, chest was clear. Liver was 4 cm palpable below costal margin and tip of spleen was palpable. Rest of the examination was unremarkable. Her laboratory examinations showed Hb level of 16 g/dl, WBC count of 49 x 10^3/ul (N=32%, L=62%) and platelet count of 341 x 10^3/ul. X-rays of chest revealed a patch of consolidation in left lower lobe and perihilar infiltrates in the right lung. Initial assessment was severe pneumonia and sepsis. Mechanical ventilation, broad spectrum antibiotics and anti-convulsants were started. After 24 hours, her condition worsened and she developed severe bronchospasm. Corticosteroids were added to relieve the bronchospasm. Condition started improving and after 72 hours, she was weaned off from the ventilator. Inspite of clinical improvement, her total leucocyte count (TLC) remained high with predominant lymphocytes. Haemophagocytosis / congenital leukemia were suspected, bone marrow biopsy and flow cytometry were done. Bone marrow biopsy revealed erythroid hypoplasia and no abnormal cells. Flow cytometry showed > 1% of double negative T-cell suggestive of autoimmune lymphoproliferative syndrome. Immunoglobulin levels done subsequently showed hypergammaglobulinemia. Hence, the diagnosis of ALPS was established after a negative bone marrow examination for leukemia and a positive result for ALPS on flow cytometry. The second case presented with anemia, thrombocytopenia starting in neonatal period followed by persistent lymphadenopathy, hepatosplenomegaly and recurrent infections which responded poorly to antibiotics. Diagnosis was delayed due to low index of suspicion, and finally achieved with multiple radiological studies, histopathology and flow cytometry.

ABSTRACT
We describe 2 cases of autoimmune lymphoproliferative syndrome (ALPS), which is a rare disorder of auto-immunity, chronic persistent or recurrent lymphadenopathy, splenomegaly, hepatomegaly and hyper gamma globulinemia (1gG, 1gA). Both cases presented in neonatal period which is a rare age of presentation in this disease. A 20 days old female neonate presented with respiratory symptoms which rapidly progressed needing ventilatory support. There was hepatomegaly and no auscultatory findings in the chest. Serial CBCs (complete blood counts) showed persistent leucocytosis with predominant lymphocytosis. Her chest X-ray showed left sided consolidation which responded poorly to antibiotics. Her prompt clinical response to steroids raised the suspicion of autoimmunity and the diagnosis was established after a negative bone marrow examination for leukemia and a positive result for ALPS on flow cytometry. The second case presented with anemia, thrombocytopenia starting in neonatal period followed by persistent lymphadenopathy, hepatosplenomegaly and recurrent infections which responded poorly to antibiotics. Diagnosis was delayed due to low index of suspicion, and finally achieved with multiple radiological studies, histopathology and flow cytometry.

was assigned. This patient is on follow-up for 18 months and doing well, except for frequent acute respiratory infections which require prompt antibiotics.

Case 2: A full term baby boy was born to unrelated couple with unremarkable SVD. He developed respiratory distress at 24 hours of age and was diagnosed and treated as RDS and improved. He developed transient thrombocytopenia which needed no treatment.

During his hospital stay, he was diagnosed to have a small atrial septal defect (ASD) and patent ductus arteriosus (PDA) on echocardiography. He was discharged on the 22nd day of life.

One week later, he reported with pallor and reduced feeding. On examination, he was anaemic, had few cervical lymph node and splenomegaly. His CBC showed a Hb level of 6.0 g/dl, hypochromia and microcytosis with a reticulocyte count of 10%. He had normal osmotic fragility and G6PD screen. A specific hemolytic anaemia could not be designated with these laboratory reports. He was given blood transfusion, discharged and follow-up was advised. In next 4 months, he reported multiple times for respiratory and gastrointestinal infections in OPD. Follow-up echocardiography revealed spontaneous closure of PDA and ASD. At 5 months of age, he presented with an ulcerated lesion at the BCG inoculation with regional lymphadenopathy. Accelerated response to BCG was suspected and INH was started. Four weeks later, he was admitted for severe respiratory distress. On examination, he had generalized lymphadenopathy, hepatosplenomegaly, bilateral crepitations and wheeze. CBC showed raised WBC with lymphocyte predominance and raised ESR. X-ray of chest revealed bilateral infiltrates with hilar lymphadenopathy. Broad spectrum antibiotics were started but the condition worsened. Reviewing the case after 5 days, diagnosis of primary progressive pulmonary TB was made and ATT was started. Condition did not improve. A pulmonologist was involved and patient was re-investigated. In addition to baseline investigation, a CT scan chest, ultrasound abdomen and CFTR gene analysis were done. CT scan chest showed right sided upper lobe consolidation and hilar lymphadenopathy. It also showed left superior vena cava (SVC) draining into the left atrium and hemizygous continued as inferior vena cava (IVC) draining into the left SVC. Ultrasound abdomen showed enlarged lymph nodes and CFTR gene analysis was negative. Axillary lymph node biopsy was done which revealed non-Hodgkin lymphoma (NHL). Patient was referred to Shoukat Khanum Memorial Hospital (SKMH) for treatment. They studied the biopsy and employed Immunohistochemical stains. The findings were CD20 positive in reactive B-cells and TdT was negative. They negated the diagnosis of lymphoma and advised repeat lymph node biopsy. Repeat biopsy was done. Immunophenotyping and flow cytometry was reported as elevated absolute T-cell count, CD4 and CD8 counts within normal limits with reverse ratio, markedly increased number of double negative T-cells, comprising of 38% of total T-cells and 19% of total cellular events. There was no evidence of acute leukemia or NHL and a diagnosis of autoimmune lymph proliferative syndrome was suggested instead.

Since he had a fulminant course of disease, child was referred back to SKMH for chemotherapy. Chemotherapy was offered by SKMH but the parents refused treatment due to poor prognosis as counseled by hospital. Patient died after 3 months.

DISCUSSION

Autoimmune Lymphoproliferative Syndrome (ALPS) also known as Canale-Smith syndrome is a rare inherited disorder of the immune system affecting both children and adults. There is abnormal lymphocyte survival caused by defective Fas mediated apoptosis. Unusually high numbers of lymphocytes accumulate in the lymph nodes, liver, and spleen leading to enlargement of these organs. In a normal person after infectious insult, the immune system down-regulates by increasing Fas expression on activated B and T-lymphocytes and Fas-ligand on activated T-lymphocytes. Fas and Fas-ligand interact to trigger the caspase cascade, leading to cell apoptosis. Patients with ALPS have a defect in this apoptotic pathway, leading to chronic non-malignant lymph proliferation, autoimmune disease, and secondary cancers.

In 1995, a molecular basis for the disease was identified as defective lymphocyte apoptosis secondary to mutations in the FAS gene. Since then, other genetic defects associated with autoimmune lymphoproliferative syndrome have been identified in the apoptotic pathway. This is the first disease known to be caused by a primary defect in programmed cell death and is the first autoimmune disease with a defined genetic basis. ALPS is characterized by lymphoproliferation and autoimmunity. Several patients present in the first year of life and most are symptomatic by 5 years of age. Lymphoproliferation is the most common clinical manifestation affecting 100% of patients, presenting as chronic non-malignant lymphadenopathy in > 90% of patients. It can be mild to severe, affecting multiple nodal groups.

These patients were unusual regarding early neonatal onset in first case presenting with respiratory complaints, fulminant course of disease with minimal lymphadenopathy and raised white cell count predominantly lymphocytes. Only one such case has been reported earlier.
The second common manifestation is autoimmunity presenting as hemolytic anaemia, thrombocytopenia and hypergammaglobulinemia. This presentation was seen in the second case presenting with hemolytic anaemia and thrombocytopenia in neonatal period. He showed lymphoproliferation later on. ALPS can affect any organ system and sometimes mimic systemic lupus erythematosus. Neurologic manifestations can take the form of autoimmune cerebellar ataxia, Guillain-Barre syndrome or transverse myelitis. Renal features can be of autoimmune glomerulonephritis or nephrotic syndrome. Autoimmune esophagitis, gastritis, colitis, hepatitis and pancreatitis can be present in some cases.

Diagnostic criteria for ALPS is given in Table I. Definitive diagnosis: required features plus one primary accessory criteria. Probable diagnosis: required features plus one secondary accessory criteria. Definitive and probable ALPS should be treated in the same manner. Autoimmune lymphoproliferative patient have been managed with corticosteroids and immunosuppressive agents cyclophosphamide, methotrexate and azathioprine. Hypersplenism may require splenectomy. Malignancies can be treated with the usual protocols used in patients unaffected by ALPS. Stem-cell transplantation is another possible option in treating the autoimmune manifestations of ALPS.

REFERENCES