CASE REPORTS

Response to Valacyclovir in an HIV-infected Girl with Epstein Barr Infection

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Received: March 21, 2011;
Initial review: April 14, 2011;
Accepted: August 02, 2011.

Response of EBV infection to valacyclovir in HIV infected children has not been reported earlier. An 8 years old HIV infected girl with undetectable viral load and normal CD4 count on regular antiretroviral therapy presented with persistent fever, lymphadenopathy and pancytopenia due to Epstein Barr virus (EBV). The child responded to valacyclovir.

Key words: *Children, EBV, HIV, Valacyclovir.*

Primary Epstein Barr virus (EBV) infection can cause leucoplakia and variety of neoplasms such as EBV lymphoproliferative syndromes, nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin's lymphoma and a subset of EBV positive gastric carcinomas especially in immunocompromised patients [1,2]. In immunocompromised hosts, it may infect liver cells, neural cells and hematological cells other than lymphocytes leading to cytopenias [3]. It has been found that in HIV infected patients, highly active antiretroviral therapy (HAART) does not lead to decrease in EBV viremia even when HIV viral load becomes undetectable or CD4 count increases [4]. We report an HIV infected girl on HAART with undetectable viral load and normal CD4 counts who developed infectious mononucleosis with peripheral cytopenia and persistent fever that responded to valacyclovir.

Case Report

An 8 years old HIV infected girl presented with fever for 1 month, cough and ear discharge for 15 days. She had been treated for pulmonary tuberculosis 2 years back. She had been on antiretroviral therapy (ART) since past 1 year consisting of Zidovudine (AZT), Lamivudine (3TC) and Efavirenz (EFV). She was febrile, had insignificant axillary and cervical lymphadenopathy, splenomegaly and oral thrush. Other systems were normal. Investigations showed anemia and leucopenia (***Table* I**). Peripheral smear did not show any atypical lymphocytes. Her Chest *X*-Ray showed haziness in right lower zone. Blood culture, peripheral smear for malaria, optiMAL test, Widal test, urine, stool, sputum examinations were normal. Ear swab grew diphtheroids. Fundus examination was also normal. Her Weil Felix test, RA factor, ANA and anti-dsDNA were negative. Serial hemograms showed a trend of gradual pancytopenia (***Table* I**). USG Abdomen showed hepatosplenomegaly. Bone marrow examination showed hypocellular marrow with early fibrosis. Her CD4 count was 406/mm^3 (27.6%) with CD4:CD8 ratio of 1.63, and HIV viral load was undetectable. Her EBV viral capsid antigen (VCA) IgM was negative (0.61 Index) and Parvovirus IgM was also negative. Renal and liver function tests were normal. She was treated with IV antibiotics and fluconazole for 14 days to which pneumonia and oral thrush responded. However, she continued to be febrile and subsequently, on Day 40 of her fever, developed large cervical and axillary lymphadenopathy. Chest *X*-ray did not show any mediastinal widening. A lymph node biopsy was done which was suggestive of necrotizing lymphadenopathy. In view of persistent fever, pancytopenia and lymphadenopathy, she was suspected to have infectious mononucleosis and her repeat CMV IgM was done, which was negative. Her EBV viral capsid antigen IgM after 15 days was positive (1.12 Index). She was then treated with valacyclovir (10 mg/kg/dose TDS) for 12 days till anti-EBV VCA-IgM became negative. EBV

TABLE I Serial Hemogram of The Print

Hemogram	Day 7	Day 15	Day 30	Day 35
Hemoglobin (g/dL)	7.7	9.8	6.4	5.8
WBC (cells/cumm)	3,400	2,600	2,100	1,300
Polymorphs (%)	40	66		
Lymphocytes (%)	56	42		
Platelets (cells/cumm)	2,46,000	2,73,000	1,83,000	59,000

nuclear antigen and EBV PCR were not done. She responded to the above treatment and fever subsided within 5 days of therapy and hemogram normalized within a week. On follow up, her hemogram continued to be normal, and she is asymptomatic and on regular ART.

DISCUSSION

An antiviral drug that could reduce the severity of acute infectious mononucleosis and potentially lower the risk for serious sequelae would be highly desirable [5].

Several antiviral drugs inhibit replication of EBV in cell culture by targeting viral DNA polymerase including acidic nucleoside analogues caciclovir, ganciclovir, penciclovir as well as their prodrug- valacyclovir, valganciclovir and famciclovir, acyclic nucleotide analogues (cidofovir and adefovir) and pyrophosphate analogues (foscarnet) [1]. Despite their potency in vitro, these drugs have limited use in vivo for treatment of acute primary EBV infection as well as EBV associated malignancies due to toxicity and non-specific antiviral activities. The reason for antiviral failure may be that most of the symptoms and signs of acute EBV are not directly due to viral cytopathology in infected tissues, but to immunopathic responses to EBV-infected cells, particularly EBV-infected B-lymphocytes and also the levels of acyclovir achieved in the oropharynx, particularly after oral administration of the drug are inadequate as compared to titres that are produced by acyclovir given intravenously [1]. Valacyclovir is the L-valyl ester of acyclovir. This modification increases acyclovir bioavailability by 3- to 5-fold compared with oral acyclovir [6]. Pharmacokinetic data suggests that dose of valacyclovir regimen of about 30 mg/kg/day gives similar AUC as that with acyclovir given 250 mg/m^2 intravenously [7]. Due to its improved absorption with higher serum concentrations, this drug is preferable to acyclovir for the treatment of EBV infections [8]. Common adverse drug reactions associated with valacyclovir therapy are the same as for acyclovir, its active metabolite, and include: nausea, vomiting, diarrhea and headache [9].

The association of HIV and Epstein-Barr virus infection has been reported in children with lymphocytic interstitial pneumonia and lymphomas [9]. Peripheral cytopenia with persistent fever has rarely been reported in HIV infected children as was seen in our patient. A study from Minnesota has found valacyclovir to be effective in treating infectious mononucleosis where the drug lowered or eliminated EBV in research subjects who took it for two weeks [10]. Similarly in our patient, cytopenias and fever responded to valacyclovir following which EBV VCA IgM also became negative signaling latency of EBV in the child.

Studies of corticosteroids in infectious mononucleosis show amelioration of acute symptoms; however, the risks of prednisolone are only justified in severe disease, for example where there is incipient airway obstruction, where steroids may reduce the need for surgical intervention to protect the airway.

There have been no reports of response of EBV infection to valacyclovir in HIV infected children. Though we had a good response to valacyclovir in our patient, detailed studies are required to determine efficacy of valacyclovir to treat complicated infectious mononucleosis in HIV infected children.

REFERENCES

1. Gershburg E, Pagano JS. Epstein–Barr virus infections: prospects for treatment. J Antimicrob Chemo. 2005;56:277-81.
2. Pagano JS, Blaser M, Buendia MA, Damania B, Khalili K, Raab-Traub N, *et al*. Infectious agents and cancer: criteria for a causal relation. Semin Cancer Biol. 2004;14:453-71.
3. Pagano JS. Epstein-Barr Virus and the Infectious Mononucleosis Syndrome. *In*: Humes HD, Dupont HL, eds. Kelley's Textbook of Internal Medicine, 4th edn. Philadelphia. Lippincott-Raven Publishers. 2000;2181–5.
4. Righetti E, Ballon G, Ometto L, Cattelan AM, Menin C, Zanchetta M, *et al*. Dynamics of Epstein-Barr virus in HIV-1-infected subjects on highly active antiretroviral therapy. AIDS. 2002;16:63-73.
5. Vezina HE, Balfour HH Jr, Weller DR, Anderson BJ, Brundage RC. Valacyclovir pharmacokinetics and exploratory pharmacodynamics in young adults with Epstein-Barr virus infectious mononucleosis. J Clin Pharmacol. 2010;50:734-42.
6. Balfour HH Jr, Hokanson KM, Schacherer RM, Fietzer CM, Schmeling DO, Holman CJ, *et al*. A virologic pilot study of valacyclovir in infectious mononucleosis. J Clin Virol. 2007;39:16-21.
7. Nadal D, Leverger G, Sokal EM, Floret D, Perel Y, Leibundgut K, *et al*. An investigation of the steady-state pharmacokinetics of oral valacyclovir in immuno-compromised children. J Infect Dis. 2002;186:S123-30.
8. Özçay F, Arslan H, Bilezikçi B, Sevmis S, Moray G, Haberal M. The role of valacyclovir on Epstein–Barr virus viral loads in pediatric liver transplantation patients. Transplant Proc. 2009;41:2878-80.
9. Carvalho AP, Gandolfi LV, Tonelli E. Epstein-Barr virus infection in children with AIDS. J Pediatr. 1998;74: 125-34.
10. Academic Health Center at the University of Minnesota. Antiviral drug effective for treatment of Infectious mononucleosis may also reduce person-to-person spread. Available at URL http://www.ahc.umn.edu//news/releases/monol121905/home.html. Accessed on February 09, 2007.

Isolated Cerebral Sinovenous Thrombosis: A Rare Case of Neonatal Antiphospholipid Syndrome

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Received: May 31, 2011;
Initial review: June 24, 2011;
Accepted: August 20, 2011.

We describe a case of neonatal cerebral sinovenous thrombosis associated with the presence of anti-phospholipid antibodies (aPL). We recommend that in all cases of neonatal thrombosis, the couple mother-infant should be extensively tested for the presence of both acquired (aPL) and congenital thrombophilia.

Key words: *Anticardiolipin, Antiphospholipid syndrome, Neonate, Thrombosis.*

Neonatal antiphospholipid syndrome (APS) is a rare clinical entity characterized by neonatal thrombotic disease due to the presence of antiphospholipid antibodies (aPL); its occurrence may depend on the transplacental transfer or on the *de novo* production of such antibodies. We describe a rare case of isolated sinovenous thrombosis associated with anticardiolipin IgG (aCL IgG) and anti-prothrombin antibodies.

CASE REPORT

A full-term neonate (birth weight 3120 grams; Apgar score 7 and 9 at 1 and 5 minutes, respectively) developed severe respiratory distress due to pneumonia soon after his delivery. During the first two weeks, his clinical condition gradually improved; serially performed cerebral ultrasound examinations were normal. On day 18, for the first time, a hyperechoic area behind the right Sylvian fissure was highlighted by routine cerebral ultrasound, in the absence of clinical manifestations. Brain magnetic resonance imaging showed a right parieto-temporal sub cortical malacic lesion associated with thrombosis of the superior sagittal sinus. The lesion extended from its medium third to the Torcular Haerophili (***Fig* 1**) and was confirmed by the magnetic resonance angiography. Coagulation profile was normal; inherited thrombophilia was negative (antithrombin, protein C and protein S were normal for the age, factor V Leiden and G20210A prothrombin gene mutation were absent and total plasma homocystein level was normal) while anticardiolipin (aCL) IgG (30 U/mL, normal <19 U/mL) and anti-prothrombin IgG antibodies (61 U/ml, normal <15 U/mL) were elevated.

His primpara mother, without familiar and personal history of thromboses and autoimmune disease, was additionally screened. Anti-prothrombin IgG and anticardiolipin IgM (aCL IgM) were positive (30 U/mL and 19 U/mL, respectively) and still present three months later.

On day 30, the neonate was discharged in good clinical conditions. Neurologic examinations, performed on the 3rd, 6th and 12th months of life showed normal neurological development.

DISCUSSION

In the neonatal period, the aPL-related thrombosis seems to be exceedingly rare, with only sixteen cases reported between 1987 and 2007 and analyzed in a recent review [1]. Arterial thromboses represent about eighty percent of the reported thromboses. To date, only three cases of venous thromboses are described: two of these affected only peripheral circulation [2, 3]; while in the third case, both the peripheral and central circulation were involved, since thrombosis of superior sagittal sinus with right middle cerebral artery infarct was detected in association to aortic and left renal artery thrombus [4].

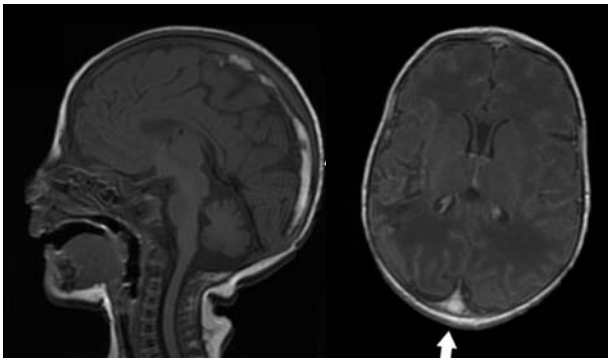

FIG. 1 *Magnetic resonance imaging of the head showing occlusion of the superior sagittal sinus.*

Cerebral sinovenous thrombosis (CVT) occurs in neonates with an incidence of at least 0.67 per 100,000 per year [5]. However, this impact is likely underestimated for several reasons as the lack of knowledge of this condition by many clinicians, the difficulty in obtaining a correct radiological diagnosis and, above all, the absence of a specific clinical presentation [6]. In recent years, the diagnosis of neonatal CVT has dramatically increased by the improved sensitivity of the neuroimaging techniques and the more frequent application of cranial imaging in the neonatal period.

It is necessary to consider several genetic and acquired conditions that are predisposing factors for thrombosis in neonatal age: inherited thrombophilias, aPL antibodies, and additional perinatal conditions asphyxia, dehydration and infection. The presence of aPL antibodies and infection are the only risk factors for thrombotic event detectable in our patient. In the present case, the occurrence of thrombotic phenomena is associated with the presence of aPL antibodies. The presence of anti-prothrombin IgG antibodies in the serum of both neonate and his mother suggests the transplacental transfer of these antibodies. Instead, the aCL IgG were positive in the neonate and negative in his mother.

Neonatal APS is rare, if not exceptional, disease; it is likely that its rarity is attributable to the fact that aPL alone are not sufficient to cause disease and others factors are probably implicated. So, in the pathogenesis of neonatal thrombosis, a second hit (usually an inflammatory event) is required as an additional prothrombotic risk factor [7,8]. In the present case, probably pneumonia was the second trigger event for the onset of thrombotic event.

This case supports a previous reported observation: not-treated women with unknown aPL are probably at greater risk to have neonatal thrombosis then women successfully treated with aspirin and low molecular weight heparin [9]. Motta, *et al.* [7] proposed that heparin, when administered to the mother during gestation, is able to bind circulating aPL, limiting the transplacental transfer to the fetal circulation and thus reducing their pathogenicity.

We recommend that in all cases of neonatal venous and/or arterial thrombosis, the mother-infant pair should be extensively tested for the presence of both acquired (aPL) and congenital thrombophilia.

Acknowledgments: Papacci Patrizia (Department of Pediatrics, Division of Neonatology, for echographic evaluation; Costantino Romagnoli (Department of Pediatrics, Division of Neonatology, Catholic University of Sacred Heart) and Angela Botta (Department of Obstetrics and Gynecology for other support.

Contributors: All authors contributed to the literature search, drafting manuscript. Final manuscript was approved by all authors.

Funding: None; *Competing interests:* None stated.

REFERENCES

1. Boffa MC, Lachassinne E. Infant perinatal thrombosis and antiphospholipid antibodies: a review. Lupus. 2007;16:634-41.
2. Contractor S, Hiatt M, Kosmin M, Kim HC. Neonatal thrombosis with anticardiolipin antibody in baby and mother. Am J Perinatol. 1992;9:409-10.
3. Hage ML, Liu R, Marcheschi DG, Bowie JD, Allen NB, Macìk BG. Fetal renal vein thrombosis, hydrops fetalis, and maternal lupus anticoagulant. A case report. Prenat Diagn. 1994;14:873-7.
4. Tabbutt S, Griswold WR, Ogino MT, Mendoza AE, Allen JB, Reznik VM. Multiple thromboses in a premature infant associated with maternal phospholipid antibody syndrome. J Perinatol. 1994;14:66-70.
5. deVeber G, Andrew M, Adams C, Bjornson B, Booth F, Buckley DJ, *et al*. Cerebral sinovenous thrombosis in children. N Engl J Med. 2001;345:417-23.
6. Ramenghi LA, Govaert P, Fumagalli M, Bassi L, Mosca F. Neonatal cerebral sinovenous thrombosis. Semin Fetal Neonatal Med. 2009;14:278-83.
7. Motta M, Rodriguez-Perez C, Tincani A, Lojacono A, Nacinovich R, Chirico G. Neonates born from mothers with autoimmune disorders. Early Human Development. 2009;85:S67-70.
8. Meroni PL, Borghi MO, Raschi E, Tedesco F. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. Nat Rev Rheumatol. 2011;7:330-9.
9. Boffa MC, Lachassinne E, Boinot C, De Carolis S, Rovere-Querini P, Avcin T, *et al*. European registry of babies born to mothers with antiphospholipid syndrome. A result update. Lupus. 2009;18:900-4.

Varied Presentation of Complicated Falciparum Malaria in a Family

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Received: June 7, 2011;
Initial review: June 29, 2011;
Accepted: August 21, 2011.

Plasmodium falciparum is known for complications with a very high mortality. We report three cases in children of the same family, two of them developed ARDS, one of them died, the third child developed hemophagocytosis and one of them also had transient myocarditis, all unusual complications of falciparum malaria.

Key words: *ARDS, Child, Falciparum, Haemophagocytosis, Myocarditis*.

Malaria due to *Plasmodium falciparum* is responsible for significant morbidity and mortality amongst nonimmune patients. ARDS may develop as a severe complication of malaria and has a high mortality rate (80%) [1,2]. Hemophagocytosis characterized by proliferation of macrophages that exhibit phagocytosis of haemopoeitic elements is commonly associated with viral infections but rarely with malaria [3]. We describe 3 patients with complicated falciparum malaria from a single family.

CASE REPORT

The *first child* was a 2 year old male, who developed fever and vomiting since 2 days followed by sudden onset breathlessness. Peripheral smear was positive for *P.falciparum* with a parasite index of 80%. The chest *X*-ray showed bilateral fluffy infiltrates and the child was unable to maintain saturation even with 60% FiO_2. The child was intubated and put on ventilator but died within a few hours due to respiratory failure. Following the death of the first child, the family was referred to us for further management.

The *second child* was a 10 year old girl brought with complaints of fever with chills and vomiting of 7 days, respiratory distress, generalized edema and jaundice of 3 days. Peripheral smear was positive for *Plasmodium falciparum*. Vitals were suggestive of hypotensive shock, there was decreased air entry bilaterally and bilateral crepitations were present; along with hepatosplenomegaly. Investigations revealed 7.2g/dL hemoglobin, platelet-35000 mm^3, total bilirubin 8.8 mg/dL (direct 7.2 mg/dL). Child was not maintaining saturation with FiO_2 0f 60% and ABG was pH-7.23, pCO_2 67.6, pO_2 64.4, HCO_3 – 27.3, SO_2 88%. Chest roentgenogram revealed bilateral fluffy infiltrates. With bilateral pulmonary infiltrates, inability to maintain saturations with a very high FiO_2 and normal cardiac function on admission, a diagnosis of ARDS was made. The child was intubated and ventilated on volume control mode with low tidal volumes and high PEEP. Intravenous artesunate was continued and circulatory support was given with dopamine. In view of persistent tachycardia, a 2D-echocardiography was done, which was suggestive of myocardial dysfunction with serial ejection fractions of 45%, 35% and 25%, which gradually improved to 55% with fluid restriction and ACE inhibitors. As the child improved, settings were reduced and child was extubated. As soon as the child stabilized, she was administered a combination of artmether and halofantrine orally for 3 days.

The *third child* was a 12 year old girl brought with complaints of weakness and fatiguability of 6 days and fever of 3 days. The peripheral smear was positive for *P. falciparum*. Pallor, icterus and hepatosplenomegaly were present. There was no respiratory distress and the chest radiograph was normal. On admission her hemoglobin was 7.4 g/dL, platelet count was 46000mm^3, and total bilirubin was 4 mg/dL. She was started on intravenous artesunate and a packed cell transfusion was given. She improved over a period of 4 days after which there was a sudden drop of hemoglobin and platelet count. Fever spikes reappeared and were present every day. Blood culture was negative and ultrasound of the abdomen was normal. She was administered artemether plus halofantrine for 3 days followed by mefloquine since her fever persisted and her hemoglobin kept dropping. Bone marrow aspiration was suggestive of hemophagocytosis. Serum ferritin was 2136 ng/dL, serum triglyceride levels were 484 mg/dL and G6PD was normal. Investigations for other etiologies of hemophagocytosis such as EBV and HIV were negative. Child improved spontaneously with supportive treatment and was discharged with normal hemoglobin and platelet counts.

DISCUSSION

ARDS is an uncommon complication in malaria but

carries a high mortality rate [4]. There is no precise data regarding the prevalence of ARDS during malaria infection; however, it is predicted nearly 20-30% of malaria patients admitted to ICU develop ARDS [5]. Proposed mechanism of development of ARDS is pulmonary vasculature dysfunction secondary to liberation of inflammatory mediators which increase vascular permeability, and parasitized RBCs' sequestration cause injury. Clinically, patients developing sudden onset tachypnea and dyspnea. Life threatening hypoxemia may develop within a few hours. Two of our patients developed ARDS, one died and other required mechanical ventilation.

Hemophagocytosis is associated with malignant, genetic, and autoimmune diseases. Viral infections as a cause are mainly limited to EBV infection. Malaria is a very rare cause and the mechanism of hemophagocytosis in malaria is unknown [3]. High levels of cytokines have been reported in malaria patients with hemophagocytosis which resolves soon after successful treatment of malaria [6-9]. Prolonged hemophagocytosis, has not been reported in patients with falciparum malaria. Once the cytokine cascade is triggered, hemophagocytosis may continue independent of the presence of the malarial parasite.

Thus, we had a family of three children, all with falciparum malaria with three unusual complications occurring in the same family.

Contributors: All authors contributed to the case report, drafting and approval.

Funding: None; *Competing interests:* None stated.

REFERENCES

1. Loser H, Schmid K, Wilfing A, Winkler S, Staudinger T, Kletzmayr J, *et al*. Experiences with severe *P. falciparum* malaria in the intensive care unit. Intensive Care Med. 2000;26:195-201.
2. Gachot B, Wolff M, Nissack G, Veber B, Vachon F. Acute lung injury complicating imported *Plasmodium falciparum* malaria. Chest. 1995;108:746-9.
3. Hamada A, Watanabe N, Tanaka H, Kobayashi A. Falciparum malaria with bone marrow abnormalities resembling malignant histiocytosis. Trans R Soc Trop Med Hyg. 1989;83:331.
4. Rowe AK, Rowe SY, Snow RW. The burden of malaria mortality among African children in the year 2000. Int J Epidemiol. 2006;35:691-704.
5. Taylor WR, Cañon V, White NJ. Pulmonary manifestations of malaria: recognition and management. Treat Respir Med. 2006;5:419-28.
6. Ohno T, Shirasaka A, Sugiyamma T, Furukawa H. Hemophagocytic syndrome induced by Plasmodium falciparum malaria infection. Int J Hematol. 1996;64:263-6.
7. Sermet-Gaudelus I, Abadie V, Stambouli F, Hennequin C, Lenoir G, Gendrel D. Haemophagocytic syndrome in Plasmodium falciparum malaria. Acta Pediatr. 2000;89:368-9.
8. Aouba A, Noguera ME, Clauvel JP, Quint L. Hemophagocytic syndrome associated with plasmodium vivax infection. Br J Haematol. 2000;103:832-3.
9. Zvulunov A, Tamary H, Gal N. Pancytopenia resulting from hemophagocytosis in malaria. Pediatr Infect Dis J. 2002;21:1086-8.

Acute Myeloid Leukemia Presenting as Obstructive Jaundice

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Received: January 29, 2011;
Initial review: February 24, 2011;
Accepted: August 30, 2011.

Jaundice as a presenting feature of pediatric acute myeloid leukemia is rare. We report two cases of AML who presented with obstructive jaundice, one with a malignant stricture at the common bile duct and other with a granulocytic sarcoma obstructing the bile duct. The prognosis is poor in these patients.

Key words: *Acute myeloid leukemia, Granulocytic sarcoma, obstructive jaundice.*

Obstructive jaundice as the presenting feature of acute myeloid leukemia (AML) is rare in children. It may be due to a stricture of the biliary tree or a granulocytic sarcoma compressing the biliary tree. We report two such cases.

CASE REPORT

Case 1: A one year old female child presented to us with pancytopenia (hemoglobin 4.5g/dL, WBC count 2100/mm^3, platelet count 13,000/mm^3). A thorough evaluation

including bone marrow study did not reveal any definite evidence of malignancy. The blood counts normalized in a month. She presented two months later, with fever, followed by increasing jaundice, pale stools and abdominal distension. She was sick, with severe pallor, jaundice, generalized edema and massive ascites. Hepatosplenomegaly could not be assessed due to the massive ascites. Laboratory investigations revealed hemoglobin 4.6 g/dL, platelet count 33000/mm^3, total count 5100/mm^3, serum bilirubin 4.8 mg/dL (conjugated bilirubin 3.6 mg/dL), SGOT 76 IU/L, SGPT 30 IU/L, ALP 263 IU/L and prothrombin time 13 seconds. Serologies for HIV and HBsAg were negative. Anti HCV titers were not done. CT scan and ultrasound scan of the abdomen showed a soft tissue lesion 6×4cm wedged between the pancreas and liver. There was moderate bilobar intrahepatic biliary radicle dilatation and common bile duct dilatation upto pancreatic segments. There was bulky celiac axis, mesenteric and retroperitoneal lymphadenopathy with moderate ascites and bilateral minimal pleural effusion. Ascitic fluid cytology showed atypical cells suggestive of leukemia/ lymphoma infiltration. Flow cytometry analysis done on the ascitic fluid revealed positivity for CD13, CD33, CD117 and CD7 markers, diagnostic of AML, possibly M5. Bone marrow study was deferred due to her poor general condition. The patient was started on subcutaneous cytosine arabinoside. In the following two weeks she improved with clearing of jaundice, reduction of abdominal distension and improvement of blood counts. A bone marrow study done showed 3% blasts with normal hemopoietic elements. Ultrasound scan of the abdomen showed disappearance of the mass and return of the biliary channels to normal size. Despite starting chemotherapy with intravenous cytosine arabinoside and daunorubicin, she developed sepsis and died.

Case 2: A previously normal 10 month old female child, presented with history of progressively increasing jaundice, clay colored stools and high colored urine of 2 months duration, followed by swellings over both parotid regions and multiple ecchymotic patches one month later. The child was sick and malnourished with deep jaundice, pallor, ecchymoses on the face and generalized lymphadenopathy. There was massive hepatosplenomegaly with liver palpable 10 cm below the right costal margin, reaching up to right iliac fossa and spleen palpable 8 cm below the left costal margin, crossing the midline beyond the umbilicus. Laboratory investigations showed hemoglobin 11.7 g/dL, platelet count 23000/ mm^3, WBC count 62000/mm^3 (Neutrophils 24%, lymphocytes 42%, myelocytes 10%, abnormal cells 24%), serum bilirubin 38mg/dL (conjugated bilirubin 30.6 mg/dL), SGOT 108 IU/L, SGPT 50 IU/L, gamma glutamyl transferase 499 U/L and LDH 1132 U. Serology for HIV and HBsAg were negative. Anti HCV titers were not done. Peripheral blood smear examination showed 33% peroxidase positive myeloid blast cells and a diagnosis of AML was made. The review of the parotid gland biopsy slides also showed infiltration by peroxidase positive myeloid blasts. Bone marrow studies could not be done due to the poor general condition of the patient. Ultrasonography and CT scan of the abdomen showed intrahepatic biliary radicle dilatation with distension of the gall bladder and dilatation of the proximal common bile duct. No mass was visualized. Magnetic resonance cholangiopancreatogram confirmed the above findings and revealed an obstruction at the level of proximal common bile duct possibly due to a malignant stricture. There was also distension of the gall bladder with dilatation of the right and left hepatic ducts and cystic duct. (***Fig.* 1**) Chemotherapy could not be instituted because of the poor general condition of the patient and she succumbed to her illness.

DISCUSSION

Obstructive jaundice as a presenting feature of pediatric malignancy is rare. Lymphoma and neuroblastoma may present with biliary obstruction. Rhabdomyosarcoma of the biliary tract may also occur. Jaundice as a presenting symptom in AML is rare. It can occur due to drug induced hepatocellular damage, post transfusion viral hepatitis, infiltration of the liver by the leukemic process or obstruction of the biliary tract. Obstruction may be due to granulocytic sarcomas compressing the biliary tree or due to stricture of the biliary tree. There are very few case reports of AML presenting as obstructive jaundice, especially in children. Jaing, *et al*. [3] have reported a 4 year old boy with extrahepatic obstruction of the biliary

FIG. 1 *MRCP showing obstruction at common bile duct with distension of gall bladder and dilatation of hepatic ducts.*

tract in AML. In their patient, on CT scan of the abdomen, there was a mass lesion at the pancreatic head associated with biliary dilatation. This patient responded well to chemotherapy, followed by bone marrow transplantation and was disease free 15 months after diagnosis.

The granulocytic sarcoma of biliary tree may be detected radiologically as a stricture or thickening of the biliary tree[1,2,4,7,8] or as a mass causing extrinsic obstruction of the biliary tree [3,5,6]. The mass obstructing the biliary tree in AML is usually a granulocytic sarcoma. This may occur concurrently with leukemia or may precede the occurrence of leukemia by weeks to months [5-8]. In our first patient, imaging studies showed a mass lesion wedged between the pancreas and liver, producing compression of the biliary channels and so we considered the jaundice to be obstructive even though the alkaline phosphatase levels were normal. The mass was a granulocytic sarcoma causing extrinsic compression of the biliary tree. In our second patient, AML presented as a stricture of the biliary tree producing obstructive jaundice. In this scenario, the major differential diagnosis to be considered is a secondary sclerosing cholangitis which in children could be due to langerhans cell histiocytosis, immuno-deficiency, sickle cell anemia or autoimmune diseases. In our patient, since the peripheral smear was diagnostic of AML, the obstruction was probably due to a malignant stricture.

Contributors: BR, AN and KP were involved in patient care. BR and AN collected data and drafted the paper. SNP was involved in the pathological diagnosis. KP critically analysed the manuscript. The final manuscript was approved by all authors. *Funding:* None; *Competing interests:* None stated.

REFERENCES

1. Mano Y, Yokoyama K, Chen CK, Tsukada Y, Ikeda Y, Okamoto S. Acute myeloid leukemia presenting with obstructive jaundice and granulocytic sarcoma of the common bile duct. Rinsho Ketsueki. 2004;45:1039-43.
2. Rajesh G, Sadasivan S, Hiran KR, Nandakumar R, Balakrishnan V. Acute myeloid leukemia presenting as obstructive jaundice. Indian J Gastroenterol. 2006;25: 93-4.
3. Jaing TH, Yang CP, Chang KW, Wang CJ, Chiu CH, Luo CC. Extrahepatic obstruction of the biliary tract as the presenting feature of acute myeloid leukemia. J Pediatr Gastroenterol Nutr. 2001;33:620-2.
4. Lee JY, Lee WS, Jung MK, Jeon SW, Cho CM, Tak WY, *et al*. Acute myeloid leukemia presenting as obstructive jaundice caused by granulocytic sarcoma. Gut Liver. 2007;1:182-5.
5. Matsueda K, Yamamoto H, Doi I. An autopsy case of granulocytic sarcoma of the porta hepatis causing obstructive jaundice. J Gastroenterol. 1998; 33:428-33.
6. King DJ, Ewen SWB, Sewell HF, Dawson AA. Obstructive jaundice-An unusual presentation of granulocytic sarcoma. Cancer. 2006; 60:114-7.
7. Gonzales-vela MC, Val-bernal JF, Mayorga M, Cagigal ML, Fernandez F, Mazzora F. Myeloid sarcoma of the extrahepatic bile ducts presenting as obstructive jaundice. APMIS. 2006; 114:666-8.
8. Sung CO, Ko YH, Park CK, Jang KT, Heo JC. Isolated biliary granulocytic sarcoma followed by acute myelogeneous leukemia with multilineage dysplasia: A case report and literature review. J Korean Med Sci. 2006;21:550-4.