Case Report

The Middle-East connection of Wolman Disease

Durjoy K. Shome, *MMBS, MD,* ***Emtethal Al-Jishi,*** *ABMP, DCH,* ***John F. Greally,*** *MD, FCAP,* ***Neelam Malik,*** *MD, MNAMS,* ***Hassan A. Zainaldeen,*** *DCH, MRCP,* ***Nagalla S. Das,*** *MBBS, MD*

ABSTRACT

The clinical, laboratory and cytological features of 2 Bahraini infants with Wolman's disease are described. While one of the cases showed the classical diagnostic features, the other case exhibited a few atypical features such as lack of adrenal calcification and unusual morphology of vacuolated marrow macrophages. Literature review shows that this disorder may not be rare in this region.

Keywords: Wolman disease, lysosomal acid lipase, adrenal calcification.

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Reduced activity of lysosomal acid lipase (LAL) isoenzyme A (synonym: acid esterase) is expressed in 2 clinical phenotypes. The relatively benign form, cholesterol ester storage disease, is usually diagnosed in adults. The severe disorder that affects infants is known as Wolman's disease.[1] In both conditions, LAL deficiency leads to the accumulation of cholesterol esters and triglycerides (the enzyme substrates) in organs and tissues.[1,2] The structural gene encoding LAL is located on chromosome 10q23.2 - q23.3.[3] Different types of LAL gene mutations that determine the clinical phenotypes have been determined.[4] Abramov et al[5] and Wolman et al[6] published the first reports of the lysosomal disorder that bears the name of Wolman. This is a rare, autosomal recessive, lipid storage disorder. Clinically, it is characterized by onset in early infancy with severe diarrhea, vomiting, mal-absorption, cachexia and hepatosplenomegaly.[1,2,5,6] A special radiologic feature is bilateral adrenal enlargement with calcification.[1,2] Hematological abnormalities consist of progressive anemia, presence of vacuolated leucocytes in peripheral blood smears (polymorphs, lymphocytes and monocytes), and lipid-laden histiocytes or foam cells in the marrow.[1,2,7] The disease is almost always fatal before the age of one year. In this report, we describe the clinical and morphological aspects of 2 Bahraini infants with this disorder.

Case Report. ***Patient one***. A 16-hour old male baby, born normally at full-term, was admitted to the neonatology unit with abdominal distention, noticed a few hours after birth and non-projectile regurgitation. There were no dysmorphic features and meconium was passed normally. Abdominal girth was 36 cm, there was no organomegaly, and the abdominal skiagram was normal. The baby improved with supportive measures and was discharged after 6 days. At the age of 9 weeks the baby was re-admitted with a history of recurrence and increasing frequency of vomiting and watery diarrhea. Examination revealed mild dehydration, pallor, abdominal

From the Department of Pathology (Shome, Das), Department of Pediatrics (Al-Jishi, Zainaldeen), and the Department of Radiology (Malik), Salmaniya Medical Complex, Department of Pathology (Greally), Arabian Gulf University, College of Medicine and Medical Sciences, Manama, Bahrain.

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Address correspondence and reprint request to: Dr. Durjoy K. Shome, Hematology Consultant, Department of Pathology, Salmaniya Medical Complex, PO Box 12, Manama, Bahrain. Fax. +973 279649. E-mail: shome@batelco.com.bh

distention, and a palpable liver 2 cm below the costal margin. Laboratory tests revealed the following: Hemoglobin 8.5 g/dl, packed cell volume (PCV) 0.26, platelets 456 x 10^9/l, white blood cell (WBC) 15.3 x 10^9/l, mean corpuscular volume (MCV) 73 fl, mean corpuscular hemoglobin (MCH) 23 pg, mean corpuscular hemoglobin concentration (MCHC) 31 g/dl, reticulocytes 1%, microcytic, hypochromic red blood cells (RBC) and target cells. Blood biochemistry tests showed normal results except for mild hypoalbuminemia (25 g/dl). Stool examination showed numerous fat globules. Blood, urine and stool cultures were negative. During the next few weeks, there was a progressive wasting with loose skin folds, wizened facies and increasing abdominal girth with intermittent passage of watery and foul-smelling stools. Radiological investigations showed distended bowel loops but no features of obstruction. No adrenal calcification was seen. Ultrasound (US) examination of the abdomen revealed splenomegaly and marked hepatomegaly with no focal lesions and diffusely increased hepatic parenchymal echogenicity suggestive of fatty infiltration. Thickened bowel walls were noted. The peripheral blood and marrow was examined considering the possibility of Wolman disease. Neutrophilic series showed mild left-shift with leukocytosis, some vacuolated lymphocytes, monocytes, polymorphs and even occasional metamyelocytes (**Figure 1**). The marrow aspirate showed a prominent increase in macrophages which had marked cytoplasmic vacuolation. Most of these cells showed the presence of well-defined, single or several vacuoles of variable sizes. Occasional macrophages resembled signet rings with giant vacuoles pushing nuclei to the periphery (**Figure 2**). These vacuoles were sudanophilic. A few foamy macrophages were present. Some myeloid cells showed cytoplasmic or nuclear vacuoles, or both. Rare erythroid precursors also showed cytoplasmic vacuoles (**Figure 1**). Serum acid lipase isoenzyme A was markedly reduced at one u/l (normal range 40-240 u/l). Assay of peripheral blood leukocytes also showed reduced acid lipase activity. Evidence of hepatocellular failure appeared after 6 weeks and was heralded by gradually rising serum bilirubin and transaminases. Despite supportive measures, the patient passed away after 8 weeks of stay in hospital.

Patient 2. A male baby, age 11 weeks, presented with a one day history of fever, watery diarrhoea and regurgitant vomiting after feeding. He was found to have abdominal distension with umbilical hernia, hepatomegaly of 7 cm and splenomegaly 6 cm below the costal margin. Initially, there was no jaundice. There were no cardiovascular, respiratory or neurological abnormalities. Investigations showed severe anemia with hemoglobin of 6.4 g/dl and markedly reduced MCV and MCH. The peripheral smear showed hypochromia, microcytosis, target cells, polychromasia and occasional nucleated RBC. Platelets and leukocyte counts were normal with a mild left-shift of neutrophils. Hemoglobin electrophoresis and high performance liquid chromatography (HPLC) revealed 6% hemoglobin Bart's. Biochemical tests showed hypoalbuminemia, raised cholesterol (6.7 mmol/l), low high density lipoproteins (HDL) (0.78 mmol/l) and hypertriglyceridemia (23.3 mmol/l). Cortisol level was raised (1088 mmol/l) and urinary vanillyl-mandelic acid (VMA) was normal. Abdominal x-ray and US studies showed bilateral adrenal enlargement with retention of the normal shapes and multiple foci of adrenal calcification (**Figure 3**). A bone marrow aspirate showed numerous foamy macrophages and vacuolated leukocytes (**Figure 4**). Although acid lipase levels could not be estimated, the diagnosis of Wolman disease with associated alpha-thalassaemia was made on the basis of the typical combination of clinical and laboratory features. As in the previous case, clinical deterioration was dominated by compromised liver function which included jaundice with rising conjugated bilirubin and transaminases, coagulopathy and thrombocytopenia. The baby passed away 6 weeks after admission.

Discussion. The clinical presentations of both patients were typical of Wolman disease: presentation in early infancy, abdominal distension, organomegaly, vomiting, diarrhea and anemia. Hepatocellular failure with hyperbilirubinemia, hypoalbuminemia and raised transaminases dominated the terminal phase with mortality within the first year of life. Massive deposition of lipids in tissues is responsible for organ failure. Symmetric enlargement with calcification of the adrenals is a diagnostic radiologic feature in most cases and is due to adrenal necrosis followed by calcium deposition.[8] However, at an early stage, only enlargement of the adrenals may be observed.[9] This sign was not observed in a minority of reported cases.[1,10] Two Bahraini babies with Wolman disease were reported in 1999.[11] Though, acid lipase levels were not determined for those cases, clinicopathologic features were sufficient for the diagnosis. Consanguinity is a common feature in all these Bahraini cases as well as in reports from the Kingdom of Saudi Arabia.[12] Reports of multiple affected children of clinically normal parents and the frequency of parental consanguinity supports an autosomal recessive mode of inheritance. Heterozygous carriers for the condition can be detected by assay of acid lipase in leukocytes or cultured fibroblasts where levels are found to be approximately half of normal.[1] Hematological features in our cases were characterized by the presence of anemia and morphological abnormalities in blood and marrow cells. In one case, association

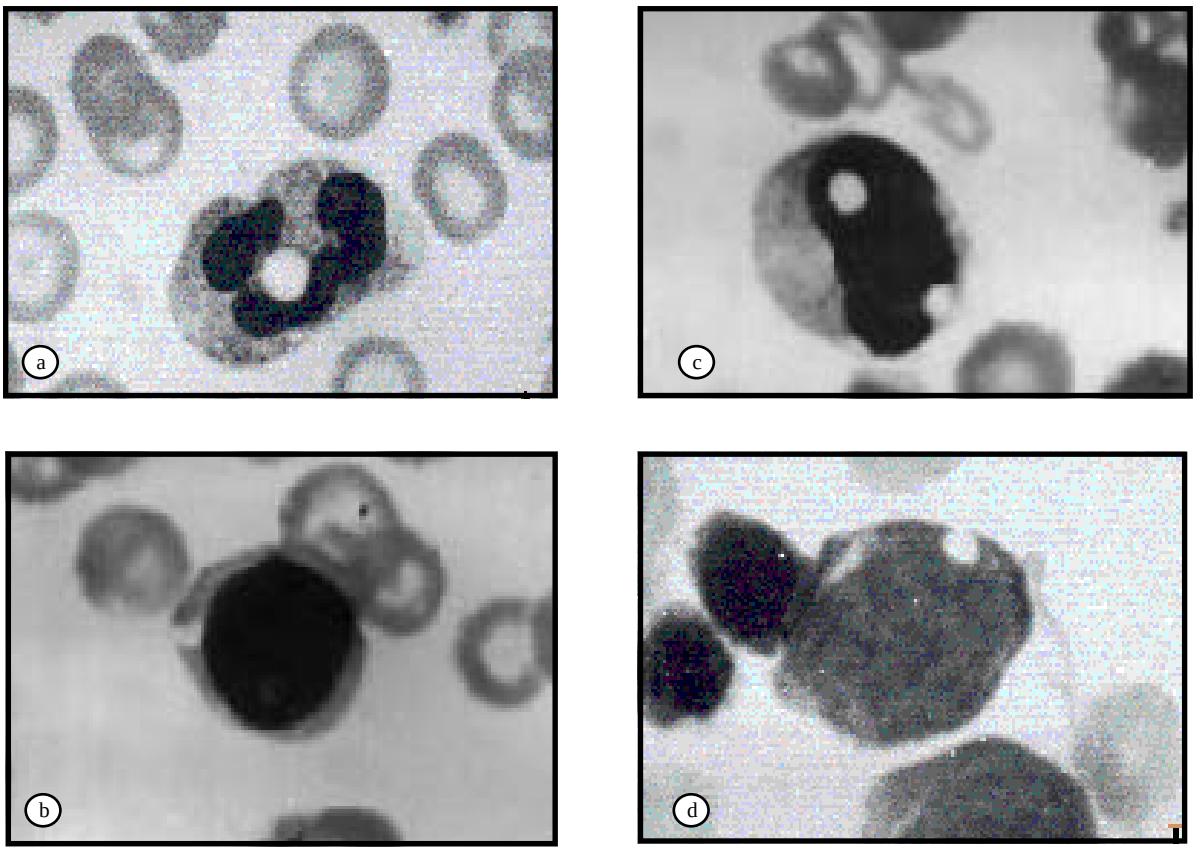

Figure 1 - Vacuolated cells in patient one showing **a)** segmented neutrophil **b)** lymphocyte **c)** monocyte **d)** proerythroblast. (Wright stain, x 1000).

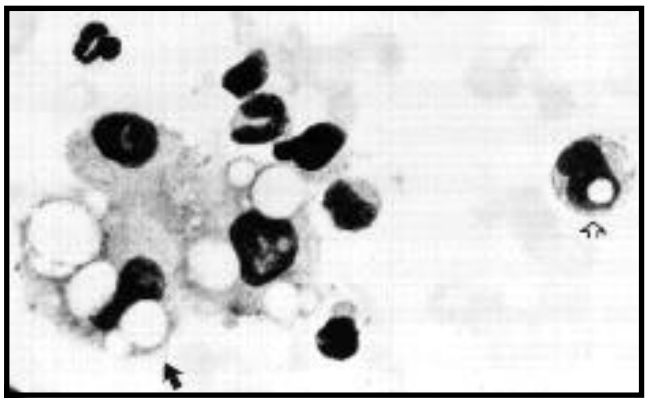

Figure 2 - Vacuolated marrow macrophages in patient one (arrow). There were relatively few, well-defined and sometimes markedly distended vacuoles. One metamyelocyte shows nuclear and cytoplasmic vacoulation (open arrow). (Wright stain, x 1000).

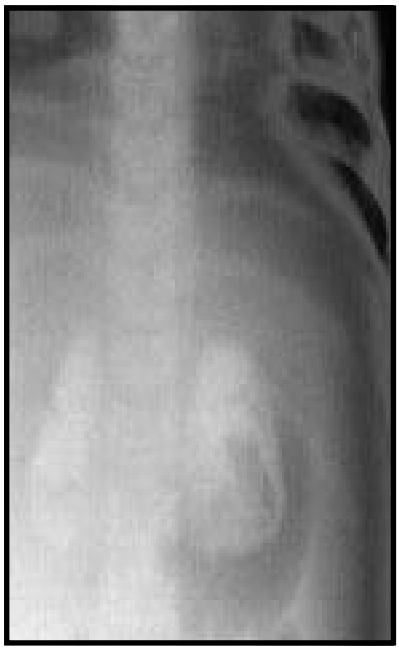

Figure 3 - Abdominal x-ray film showing bilateral enlarged and calcified glands in patient 2.

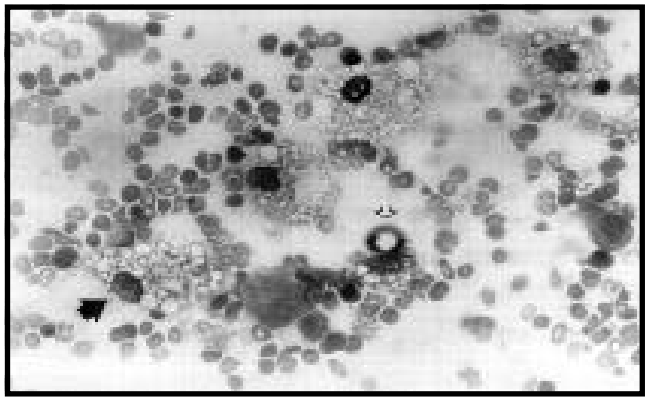

Figure 4 - Typical foam cells (arrow) and a vacuolated neutrophil band (open arrow) seen in the bone marrow of patient 2. (Wright stain x 400).

with alpha-thalassemia accentuated the anemia. Vacuolated leukocytes were seen in peripheral blood and marrow smears. This was more obvious in peripheral blood and bone marrow neutrophils, monocytes and macrophages. Vacuolated lymphocytes, erythroid and myeloid precursors were present in small numbers. Infiltration of marrow by foamy macrophages, has been commonly noted as a characteristic feature of the disorder. These cells were abundant in patient 2. However, in patient one, the morphology of most macrophages was somewhat different. This was typified by the presence of fewer but well delineated and sometimes prominently distended vacuoles that occasionally pushed the nucleus to the periphery (**Figure 2**). This morphological variation has not been emphasized previously. Since this case presented very early (soon after birth) and lacked calcified adrenals, it is possible that this feature may be related to earlier presentation. As there is no specific therapy, the prognosis for patients with Wolman disease is poor. Recently, successful therapy by bone marrow transplantation has been reported.[13] Lysosomal acid lipase-gene transfer is a future possibility.[14] Wolman disease has been reported from many countries.[1] However, there appears to be a concentration of cases reported from the middle-east region. These relate to Jews of Iraqi origin, Arabs of the Galilee region, Saudi Arabians and one Jordanian case.[1,12,15-17] The occurrence of this disorder in Bahrain appears to confirm the impression that the disorder may not be rare in this population. Awareness of the clinical, cytologic and demographic features is important for practising pediatricians and pathologists in this region as the diagnosis can be made on the basis of clinical features and simple radiological and laboratory investigations in most instances.

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References

1. Assmann G, Seedorf U. Acid lipase deficiency: Wolman disease and cholesteryl ester storage disease. In: Scriver CR, Beaudet AL, Sly SW, Valle D, editors. The metabolic and molecular genetic bases of inherited disease. New York (NY): McGraw Hill Inc; 1995. p. 2563-2587.
2. Kolodny EH, Lebron D. Storage diseases of the reticuloendothelial system. In: Nathan DG, Orkin SH, editors. Hematology of infancy and childhood. 5th ed. Philadelphia (PA): WB Saunders Company; 1998. p. 1461-1507.
3. Anderson RA, Rao N, Byrum RS, Rothschild CB, Bowden DW, Hayworth R et al. In situ localisation of the genetic locus encoding the lysosomal acid lipase/cholesteryl esterase (LIPA) deficient in Wolman disease to chromosome 10q23.2-23.3. *Genomics* 1993; 15: 245-247.
4. Anderson RA, Bryson GM, Parks JS. Lysosomal acid lipase mutations that determine phenotype in Wolman and cholesteryl ester storage disease. *Mol Genet Metab* 1999; 68: 333-345.

5. Abramov A, Schorr S, Wolman M. Generalised xanthomatosis with calcified adrenals. *J Dis Child* 1956; 91: 282-286.
6. Wolman M, Sterk VV, Gatt S, Frenkel M. Primary familial xanthomatosis with involvement and calcification of the adrenals. Report of two more cases in siblings of a previously described infant. *Pediatrics* 1961; 28: 742-747.
7. Roytta M, Fagerlund AS, Toikkanen S, Salmi TT, Jorde LB, Forsius HR et al. Wolman disease: morphological, clinical and genetic studies on the first Scandinavian cases. *Clin Genet* 1992; 42: 1-7.
8. Fitoussi G, Negre-Salvayre A, Pieraggi MT, Salvayre R. New pathogenetic hypothesis for Wolman disease: possible role of oxidised low-density lipoproteins in adrenal necrosis and calcification. *Biochem J* 1994; 301: 267-273.
9. Nyhan WL, Ozant PT. Atlas of metabolic diseases. 1st ed. London (UK): Chapman and Hall Medical; 1998. p. 586-591.
10. Schaub J, Janka GE, Christomanou H, Sandhoff K, Permanetter W, Hubner G et al. Wolman's disease: clinical, biochemical and ultrastructural studies in an unusual case without striking adrenal calcification. *Eur J Pediatr* 1980; 135: 45-53.
11. Aldeen HAZ, Al-Hilli F, Mohammad AM, Jamsheer NS, Romani KHR. Wolman's disease. The first two cases from Bahrain. *Bahrain Medical Bulletin* 1999; 21: 24-26.
12. Al Essa M, Nounou R, Sakati N, Le Quesne G, Joshi S, Archibald A et al. Wolman's disease: The King Faisal Specialist Hospital and Research Centre experience. *Annals of Saudi Medicine* 1998; 18: 120-124.
13. Krivit W, Peters C, Dusenbery K, Ben Yosef-Y, Ramsay NK, Wagner JE et al. Wolman disease successfully treated by bone marrow transplantation. *Bone Marrow Transplant* 2000; 26: 567-570.
14. Tietge UJ, Sun G, Czarnecki S, Yu Q, Lohse P, Du H et al Phenotypic correction of lipid storage and growth arrest in Wolman disease fibroblasts by gene transfer of lysosomal acid lipase. *Hum Gene Ther* 2001; 12: 279-289.
15. Wolman M. Wolman disease and its treatment. *Clin Pediatr* 1995; 42: 207-212.
16. Raafat F, Hashemian MP, Abrishami MA. Wolman's disease: report of two new cases with a review of the literature. *Am J Clin Pathol* 1973; 59: 490-497.
17. Kamaliau N, Dudley Jr AW, Beroukhim F. Wolman's disease with jaundice and subarachnoid hemorrhage. *Am J Dis Child* 1973; 126: 671-675.