Novel association of metastatic Crohn's disease and Wolman disease

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INTRODUCTION

Metastatic Crohn's disease (MCD) is a rare manifestation of Crohn's disease (CD) defined by noncaseating, cutaneous granulomatous lesions that are not contiguous with intestinal CD.[1] Although MCD is well recognized in adults, it is exceedingly rare in children.[1] The onset of cutaneous lesions may develop simultaneously or precede gastrointestinal (GI) disease, with most cases of MCD presenting prior to the diagnosis of GI CD.[1] We describe a novel association of MCD with Wolman disease. Wolman disease is a rare, autosomal, recessive lysosomal storage disorder presenting in infancy.[2] It occurs due to a mutation in the *LIPA* gene, which leads to a deficiency in lysosomal acid lipase, an enzyme essential for the metabolism of triglycerides and cholesterol esters.[2] A deficiency in this enzyme causes the accumulation of triglycerides and cholesterol in the viscera, such as the liver, spleen, adrenals, lymph nodes, and bowel.[2] Infants generally present during the second to third month of life, with features of abdominal distension, malnutrition, diarrhea, and failure to thrive.[2]

Abbreviations used:

CD:	Crohn's disease
GI:	gastrointestinal
MCD:	metastatic Crohn's disease

CASE DESCRIPTION

A 39-month–old girl was diagnosed with Wolman disease at the age of 4 months by molecular testing. The disease manifested as hepatosplenomegaly, adrenal calcification, and severe failure to thrive. Plain radiographs of the abdomen showed symmetrically enlarged adrenal glands with maintained triangular shape and extensive calcifications. An ultrasound of the abdomen revealed hepatomegaly with fatty infiltration, splenomegaly, and enlarged adrenal glands with calcification and multiple enlarged mesenteric lymph nodes. A *LIPA* nucleotide sequence analysis showed the homozygous variant c.260G>T (Gly87Val), and biochemical testing of lipase A activity by liquid chromatography mass spectrometry showed <8.0 limit of detection (reference, ≥32.5 mol/L/h), which are, collectively, diagnostic of Wolman disease.

The patient presented with swelling of the labia majora for 2 months. Examination revealed marked erythema and edema of the labia majora, and the perianal area had multiple erythematous and macerated fissures near the anal orifice. The parents were consanguineous but healthy, with unremarkable family history (Fig 1). Histologic examination of a perianal skin punch biopsy specimen showed epidermal hyperplasia and diffuse, noncaseating granulomatous dermatitis, with dense plasma cell infiltrates extending to the subcutaneous tissue, highlighting the likelihood of MCD on the basis of clinical and histopathologic correlation (Fig 2). The patient's fecal calprotectin level was 382 ug/g (reference, <200 ug/g). GI endoscopy revealed esophageal intraepithelial lymphocytosis, chronic inactive

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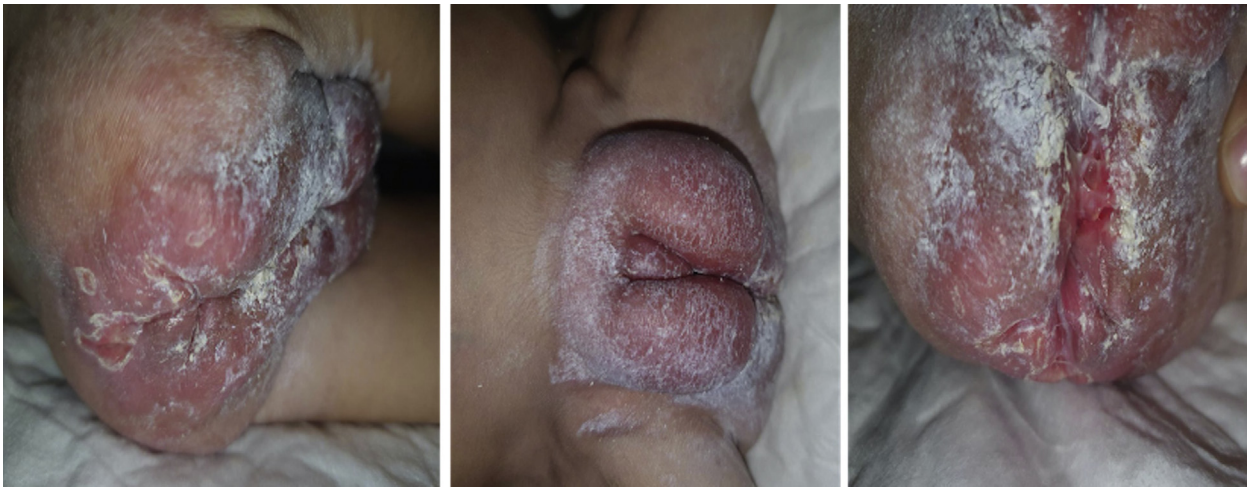

Fig 1. Patient at initial presentation. Examination revealed marked erythema and edema of the labia majora, and the perianal area had multiple erythematous and macerated fissures near the anal orifice.

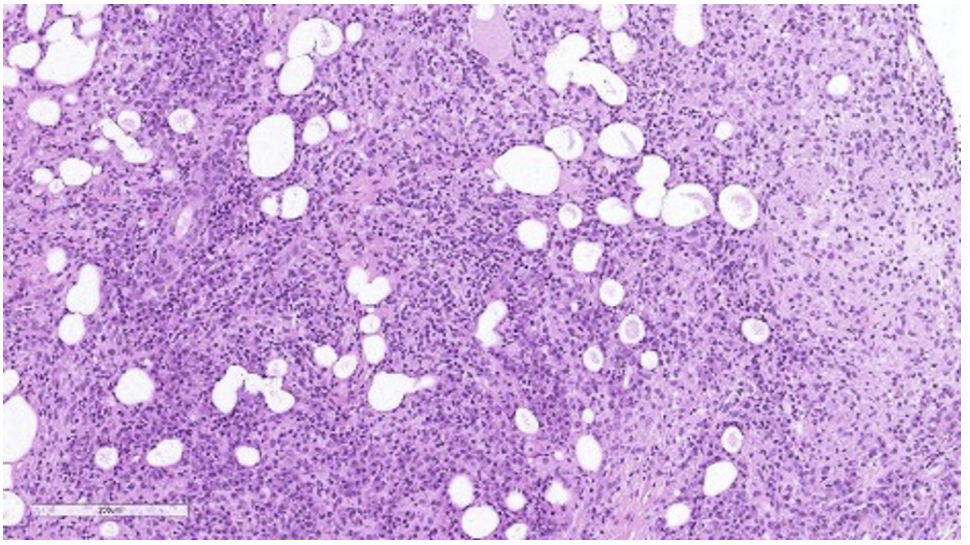

Fig 2. Histologic examination of perianal skin punch biopsy showed epidermal hyperplasia and diffuse noncaseating granulomatous dermatitis, with dense plasma cell infiltrates extending to the subcutaneous tissue.

gastritis, and multiple duodenal and colonic superficial aphthous ulcers. A histologic examination of the colonic biopsies showed expansion of the lamina propria with foamy histiocytes and xanthoma cells, consistent with Wolman disease, with no evidence of the noncaseating granuloma that is characteristic of GI CD.

Upon initial presentation, the patient was treated with a 14-day course of a topical combination of miconazole and hydrocortisone ointment twice daily, then 0.1% topical tacrolimus ointment twice daily, with mild improvement (Fig 3). Unfortunately, the patient suffered from cardiopulmonary arrest secondary to multiorgan failure, with a severe electrolyte imbalance and hypotension due to refractory septic shock, and died a few months after the first dermatology visit.

DISCUSSION

The case report presents a novel association of MCD in a patient with Wolman disease; to our knowledge, there is no such association in the literature. Wolman disease is a rare, autosomal, recessive lysosomal storage disorder that occurs due to a *LIPA* gene mutation, which leads to a deficiency in the lysosomal acid lipase and causes

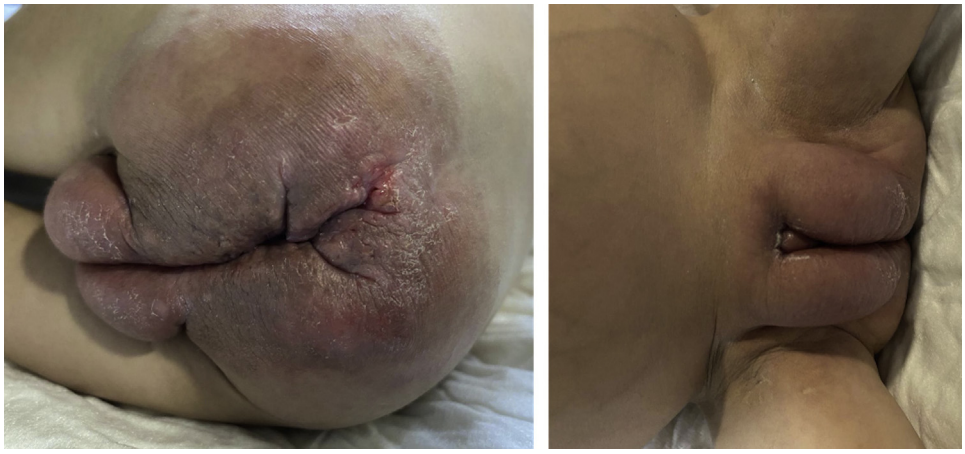

Fig 3. Patient, a few weeks posttreatment, with mild improvement of skin lesions noted.

the accumulation of triglycerides and cholesterol in the viscera. The only skin manifestation reported in Wolman disease is a yellowish tint (jaundice) from liver fibrosis as the disease progresses.[3] Although there were no reports of CD in patients with lipid storage disease, previous reports demonstrate notable differences in lipid metabolism-related pathways in CD. The most marked differences occur in fatty acids, acylcarnitine metabolites, sphingolipids, and bile acid metabolism. Moreover, growing evidence suggests that lipid metabolism, amino acid deficiency, and the loss of energy homeostasis play important roles in inflammation and may have significant implications for the pathogenesis of inflammatory bowel disease.[4] The prognosis of Wolman disease is quite poor, with most patients dying within the first months of infancy, especially if not diagnosed and treated early.[2]

MCD appears as nonspecific skin lesions with the histologic findings of noncaseating granulomas, with no contiguity between the skin lesions and intestinal involvement.[5] MCD is known as a great mimicker and is often misdiagnosed. This results from the variability in morphologic presentation and similarities to other dermatoses. Cutaneous findings may precede, develop concurrently with, or follow GI involvement.[6] A detailed history and physical examination, including a thorough skin examination, should be conducted to help guide diagnostic possibilities. However, a biopsy is ultimately required for a definitive diagnosis. The most common age of onset of MCD among pediatric patients is 10 to 14 years old, with remarkable involvement of the genital area.[7] Our patient presented with notable GI manifestations, as biopsies demonstrated the changes of Wolman disease but the absence of noncaseating granulomas. This is attributed to the cutaneous involvement that likely preceded the onset of GI involvement by CD. To date, there are no randomized clinical trials of therapeutic options for MCD. However, several drugs have been reported in the literature, including topical steroids, oral steroids, metronidazole, azathioprine, sulfasalazine, 6-mercaptopurine, and infliximab. Our patient was treated with a 14-day course of a topical combination of miconazole and hydrocortisone ointment twice daily, then 0.1% topical tacrolimus ointment twice daily, with several measurements of the whole blood trough level. Mild-to-moderate clinical improvement was noted. Several reports have demonstrated spontaneous resolution; however, the majority of MCD cases are persistent.[8] The prognosis of a cutaneous manifestation is similar to CD, in which childhood-onset inflammatory bowel diseases have an increased risk of mortality compared to the general population.[9,10] MCD is likely underdiagnosed given its variable clinical manifestations, and, therefore, its exact prevalence in pediatric patients is unknown. A thorough history, skin examination, and biopsy are crucial for a definitive diagnosis and to avoid a delay in treatment and substantial morbidity. Further research is required to establish the relationship between abnormal lipid metabolism and MCD and to assess the therapeutic options.

Conflicts of interest

None disclosed.

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