Ultrasonographic findings in hyperimmunoglobulin D syndrome: a case report

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Abstract

Hyperimmunoglobulin D syndrome due to mevalonate kinase deficiency is a rare autoinflammatory disease with digestive tract involvement. We report an 11-year female child who has presented since the age of 1 year, bouts of fever, rash, joint swelling, pulmonary consolidation, lymph node involvement and hepatosplenomegaly. Hyperimmunoglobulin D and increased urinary mevalonic acid were detected. The ultrasonographic features of hepatosplenomegaly ranged from increment in size to pseudotumoral involvement, with hypoechogenic masses without apparent wall. Abdominal CT during a disease flare showed hypodense, hypoenhancing nodular lesions, suggesting metastases. Nevertheless, a thorough search for malignancy was negative and the masses disappeared after the flare. Mevalonate kinase deficiency may add to the causes of hepatosplenic and pulmonary inflammatory pseudotumors.

Keywords: hyperimmunoglobulinemia D; mevalonate kinase deficiency; inflammatory pseudotumor; pulmonary ultrasonography.

Introduction

Mevalonate kinase deficiency (MVK) is an autosomal recessive autoinflammatory metabolic syndrome, due to mutations of the *MVK* gene on the 12q24.3 chromosome, encoding mevalonate kinase. Depending on the amount of functional enzyme, MVK expression ranges from hyperimmunoglobulinemia D (HIDS), characterized by periodic fever with rash, adenomegaly, abdominal pain, and diarrhea, to mevalonic aciduria, with dysmorphism, hepatopathy, and neurologic dysfunction [1,2].

We present the ultrasonographic findings in a pediatric case with recurrent fever, hepatomegaly and/or splenomegaly, and pulmonary consolidation, finally proven to have HIDS/MVK.

Case report

An 11-year girl, first child of unrelated healthy parents, with no dysmorphic features and normal neurologic development, was repeatedly seen since the age of 11 months for episodes of fever lasting for 4-6 days, pharyngeal erythema, aphthae, cervical lymph nodes enlargement, pneumonia, abdominal pain, diarrhea and rash. Laboratory revealed during these flares, acute phase reactants (erythrocyte sedimentation rate [ESR] up to 140 mm/h, C-reactive protein 36 mg/dl), leukocytosis with neutrophilia, increased ferritin, normal liver enzymes, and no cholestasis markers. ESR remained elevated between the attacks (ESR around 40 mm/h). IgD values were found repeatedly high (up to 1570 IU/mL, normal

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range <100 IU/mL), parallel with high IgA values. Urinary mevalonic acid was 10.9 mmol/creatinin mol (normal range <1.3 mmol/creatinin mol). The genetic tests were not available.

During follow-up the hepatosplenic and lymph node involvement raised important differential diagnosis problems. A liver biopsy at the age of 18 months had revealed very large hepatocytes with folded cytoplasm and PAS-positive intracytoplasmatic granules, sinusoid capillarisation and some fibrotic deposition in the portal spaces. Abdominal ultrasonographic follow-up was performed using a Toshiba Xario V 2.0 ultrasound machine with 8-14 MHz linar probe and 3-6 MHz convex probes. Splenomegaly and/or hepatomegaly were almost constant findings during the flares, sometimes with reversible hyperechoic images without acoustic shadowing. Ultrasonography also detected other sites of inflammation (articular, sinusal, or pleuropulmonary). Enlarged lymph nodes were found during attacks, rarely with hyperechoic center evoking inflammation and necrosis, or pseudotumoral appearance (Table I).

During a severe acute inflammatory episode, at the age of 11, several hypoechoic pseudotumoral hepatosplenic masses without apparent wall were detected (fig 1-2). The thoraco-abdominal CT (T1-weighted) revealed similar hypodense, hypoenhancing nodular lesions, suggestive of metastases, disseminated in the liver and spleen. However, all the lesions in the liver and spleen completely disappeared spontaneously within 2 months, and were therefore considered to be pseudotumors.

During the same described flare, lung ultrasonography found fluid in the left pleural space and areas of consolidation (fig 3). Extensive screening for infection was nevertheless negative and empiric antibiotic therapy unsuccessful. The lesions were completely reversible after corticosteroids.

After the diagnosis of HIDS/MVK, therapy consisted of corticosteroids during flares. Other medications such as anti-IL-1 (anakinra, canakinumab) and anti-TNF were not employed due to the current lack of national reimbursement for this diagnosis.

Table I. Ultrasonographic hepatosplenic and lymph node findings during longitudinal follow-up.

Age	Liver	Spleen	Lymph nodes
11 mo	normal	normal	
1 y	normal	100 mm, hyperechoic dots, without shadow	
18 mo	LNB, RL 100 cm	80 mm	
3 y	Hepatosplenomegaly, normal echo-structure, RL 100 mm, LL 74/43 mm, CL 18 mm	105 mm	
5 y	RL 120/107 mm, LL 45 mm, CL 23 mm (>)	Splenomegaly (115 mm)	Hepatic hilum, mesenteric and right iliac (<15 mm)
6 y	RL 130 mm, CL normal	120 mm	Cervical, submandibular, mesenteric, iliac (<15 mm)
7 y	RL 115 mm, LL 42 mm, CL 22 mm	100 mm	Mesenteric, right iliac fossa (14/7 mm), right jugular block (25 mm)
8 y	Normal	Normal	Hepatic hilum (14 mm) mesenteric (11 mm)
10 y	RL 140 mm in renal axis, LL 43 mm, CL 28 mm	115 mm	Cervical (several vascular poles, increased stiffness)
11 y onset	RL 148 mm, inferior rounded margin; focal inhomogenous hypoechoic areas without apparent wall, 6-7 mm diameter, with no vascularisation, suggesting granulomas or metastases	Splenomegaly 130-150 mm, with similar inhomogenous hypoechoic areas without apparent wall, 6-7 mm diameter, with no vascularisation	Intrapleural lymph nodes (right 12/7 mm, left 8/4 mm) Hepatic hilum (9/12 mm- up to 15 mm)
after 2 wks*	RL 155 mm, rounded margin; a single hypoechoic lesion	123 mm, without focal hypoechoic areas	Mesenteric lymph nodes, up to 11 mm, no hepatic hilum adenomegaly
after 5 wks*	RL 145 mm, normal margin, without focal lesions	127-138 mm, a single 4 mm hypoechoic area	Mesenteric lymph nodes up to 13 mm
after 7 wks*	RL 140 mm, normal structure	110 mm, normal structure	No
after 4 mo*	RL 143 mm	118 mm	No

LL – left lobe, RL –right lobe, CL – caudate lobe, LNB – liver needle biopsy, *from flare onset, y – years, mo – months, wks – weeks

Fig 1. Liver US examination at the age of 11: a) Transverse section on the left liver lobe revealed a small hypoechoic lesion, without apparent wall; b) Control after 4 months did not detect focal liver lesions.

Fig 2. Spleen US at the age of 11, coronal section on the left flank: a) There are two lesions with the same US pattern as the liver lesion described in fig. 1 (arrows); b) 4 months later the spleen parenchyma had a homogenous structure.

Discussions

MVK affects at least 300 people worldwide, most of them with HIDS [2]. Many cases start before one year of age, but later onset is also reported [2,3]. HIDS flares are triggered by vaccination, infections, minor trauma,

Fig 3. Pleuropulmonary US aspects at the age of 11: a) Longitudinal section of the left posterior hemithorax, subscapular area showed fluid and absence of the “A lines” (between calipers) b) Longitudinal US scan of the left posterior hemithorax (examination was done after 3 weeks) detected normal “A lines” (white arrowheads), representing normal lung parenchyma and very thin pleural effusion (between calipers).

stress, etc. The diagnosis is sustained by high IgD and IgA and elevated urinary mevalonic acid, and confirmed genetically whenever possible [1,2].

Gastrointestinal inflammation is frequent in MVK [3,4]. Generally, hepatosplenomegaly is detected in mevalonic aciduria, along with dysmorphic features and severe neurologic impairment, absent in our case [5]. Liver involvement in MVK may manifest as neonatal hepatitis, hepatomegaly or hepatosplenomegaly, cholestatic liver dysfunction, hepatic fibrosis, or even hepatic failure [6-8]. MVK mimicks metabolic, infectious, chromosomal, hematologic, or neoplastic diseases [1,3]. Liver biopsy reveals an inflammatory lymphocytic infiltrate, such as in our case, associated with portal fibrosis [7] or histiocyte infiltration with hemophagocytosis [8].

There are few data regarding ultrasonography in pediatric patients with HIDS/MVK, although it may be

Table II. Potential uses of ultrasonography in children with mevalonate kinase deficiency

Procedure	Possible findings in MVK
Abdominal US	Hepatosplenomegaly (with normal or inhomogenous structure) Hepatic fibrosis Pseudotumoral masses (focal inhomogenous hypoechoic areas without apparent wall and no vascularisation) Renal angiomyolipoma Abdominal lymph nodes enlargement Peritonitis, ascites, pelviperitonitis
US-guided biopsy	Inflammation, fibrosis
Cervical lymph node US	Lymph nodes enlargement (unilateral or bilateral) Pseudotumoral aspects (increased vascularisation and stiffness, multiple vascular poles)
Colonic hydrosoundography	Increased wall thickness of the terminal ileon and colon Altered stratification
Pulmonary US	Pleuritis/pleuresia Pulmonary consolidation Pleural and/or pulmonary pseudotumoral irregular hyperechic masses (pseudotumors)
Maxillary US	Sinusitis
Articular US	Synovitis (knee, tibio-tarsal) Erosions (rarely)

a valuable tool (table II) as heterogenous hepatosplenomegaly may be seen [7]. In our patient, the hypoechoic hepatosplenic masses with rapid regression were likely inflammatory pseudotumors, mass-forming lesions characterized by a prominent inflammatory infiltrate. Liver pseudotumors are hypoechoic or hyperechoic masses, with hypoattenuating parenchyma on unenhanced CT, and hypointense lesions on T1-weighted and hyperintense on T2-weighted images after contrast administration [9].

Another peculiarity in our case was the recurrent pulmonary consolidation, uncommon in HIDS. The differentiation from infection was difficult, inasmuch as the defense against *Pneumococcus* is impaired in HIDS/MVK, and the attacks are usually triggered by infections, sometimes occult [3,6]. Nevertheless, the negative exhaustive search for infections and the remission after corticosteroids pointed to lung inflammatory pseudotumors [10].

In conclusion liver and splenic involvement in MVK may be misleading. Ultrasonography is an important tool for follow-up, mainly in children. The diagnosis of HIDS/MVK could be included in the differential list of hepatosplenomegaly, adenomegaly, and recurrent pulmonary consolidation, as well as in the lymphoma mimicry. Also, HIDS/MVK may be another cause of inflammatory pseudotumors, with spontaneous resolution.

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