World Journal of Radiology

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World J Radiol 2024 August 28; 16(8): 371-374

DOI: 10.4329/wjr.v16.i8.371

ISSN 1949-8470 (online)

LETTER TO THE EDITOR

Plea to radiologists: Please consider Mahvash disease when encountering an enlarged pancreas

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Specialty type: Radiology, nuclear medicine and medical imaging

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade B
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Suvvari TK

Received: March 25, 2024
Revised: August 15, 2024
Accepted: August 19, 2024
Published online: August 28, 2024
Processing time: 156 Days and 7 Hours

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Abstract

Radiologists play a key role in establishing an early and accurate diagnosis, especially for rare diseases. Mahvash disease (OMIM 619290) is an autosomal recessive hereditary disease caused by inactivating mutations of the glucagon receptor and its main clinical consequences are pancreatic neuroendocrine tumors and in some cases, porto-sinusoidal vascular disease and portal hypertension. Untreated Mahvash disease can be lethal. The diagnosis of Mahvash disease has almost always been delayed in the past due to radiologists' unawareness of or unfamiliarity with the unique imaging features of Mahvash disease which are moderately to enormously enlarge pancreas with preserved pancreas contour and parenchyma without vascular involvement or lymphadenopathy. These features help differentiate Mahvash disease from other etiologies of diffusely enlarged pancreas such as diffuse pancreatic ductal carcinoma, diffuse pancreatic lymphoma, and autoimmune pancreatitis. Invoking Mahvash disease in the differential diagnosis of an enlarged pancreas has recently been shown to facilitate early diagnosis. To prevent missing the diagnosis of this significant disease, I sincerely ask radiologists to consider Mahvash disease in their differential diagnoses of diffusely enlarged pancreas.

Key Words: Mahvash disease; Pancreas imaging; Enlarged pancreas; Pancreatic ductal carcinoma; Pancreatic lymphoma; Autoimmune pancreatitis

Core Tip: Mahvash disease is a potentially lethal, autosomal recessive hereditary disease of pancreatic neuroendocrine tumors and inborn error of metabolism. The diagnosis of Mahvash disease has been delayed in the past largely due to radiologists' unawareness of or unfamiliarity with the unique imaging features of Mahvash disease. On the other hand, Mahvash disease can be readily diagnosed once its imaging features are appreciated. To prevent missing the diagnosis of this interesting disease, radiologists should consider Mahvash disease in their differential diagnoses of diffusely enlarged pancreas.

Citation: Yu R. Plea to radiologists: Please consider Mahvash disease when encountering an enlarged pancreas. *World J Radiol* 2024; 16(8): 371-374
URL: https://www.wjgnet.com/1949-8470/full/v16/i8/371.htm
DOI: https://dx.doi.org/10.4329/wjr.v16.i8.371

TO THE EDITOR

Radiologists play a key role in establishing an early and accurate diagnosis[1]. Radiologists' role in diagnosing rare diseases is particularly important as some rare diseases exhibit quite unique imaging features that few other diseases would share so that radiologists can make an early call of the rare diseases in the imaging differential diagnosis[2]. If the attending radiologist is not aware of the imaging features of a rare disease, however, the rare disease will not be listed in the differential diagnosis thus a cognitive diagnostic error ensues[3]. This kind of cognitive imaging diagnostic error is especially common in the imaging diagnosis of new and rare diseases, such as the Mahvash disease (OMIM 619290).

The Mahvash disease is an autosomal recessive hereditary disease caused by inactivating mutations of the glucagon receptor[4]. It was first reported in 2008[4]. Approximately 15 cases of confirmed Mahvash disease have been described so far including a recent high-profile case published in the *NEJM*[5,6]. The Mahvash disease is characterized by hyperglucagonemia without glucagonoma syndrome, hyperaminoacidemia, pancreatic α cell hyperplasia, and pancreatic neuroendocrine tumors[4]. Severe Mahvash disease with complete loss of glucagon receptor activity can cause porto-sinusoidal vascular disease and portal hypertension which are curable by liver transplant[5,6]. The Mahvash disease is thus both a hereditary tumor syndrome and an inborn error of metabolism. Untreated Mahvash disease can be lethal[4].

The diagnosis of Mahvash disease has almost always been delayed. Patients with Mahvash disease most frequently present with vague abdominal symptoms so they receive abdominal imaging[4]. Since its discovery, the first suspicion of Mahvash disease has been largely based on imaging findings suggestive of pancreatic neuroendocrine tumors. Laboratory testing of pancreatic hormones then reveals massive hyperglucagonemia. In the absence of glucagonoma syndrome, the diagnosis of Mahvash disease is invoked. If glucagon is not tested, the diagnosis of Mahvash disease is missed, which has happened in a number of potential but likely cases of Mahvash disease; in all these cases, typical imaging features of Mahvash disease are clearly present but Mahvash disease is not considered by radiologists[7-11].

To prevent missing such a significant and lethal disease, I make a plea to radiologists here to please consider Mahvash disease when they encounter its imaging features. The imaging features of Mahvash disease are quite unique and include diffusely enlarged pancreas with or without pancreatic masses[4]. The diffuse pancreatic enlargement is due to expansion of both endocrine (mainly α cells) and exocrine (mainly acinar cells) components of the pancreas and distributes evenly throughout the pancreas[4]. The diffuse pancreatic enlargement can be enormous and may be accompanied by single or multiple lesions of pancreatic neuroendocrine tumors (Figure 1). In the early stage of Mahvash disease, such lesions may be absent. Multiple punctate calcifications are frequently found in the pancreas (Figure 1). Other abdominal organs are grossly normal on imaging in Mahvash disease.

Needless to say, Mahvash disease cannot be diagnosed based on imaging features alone and diffuse enlargement of pancreas can be seen in other pancreatic diseases such as diffuse pancreatic ductal adenocarcinoma, diffuse pancreatic lymphoma, and autoimmune pancreatitis[12-14]. Several distinct differences of these entities on imaging provide valuable clues to the differential diagnosis (Table 1). The pancreas enlargement can be enormous and but always even with preserved normal pancreatic contour in Mahvash disease while the degree of pancreatic enlargement is less extensive with loss of the normal pancreatic contour (sausage-shape) in the other 3 diseases. The pancreas parenchyma in Mahvash disease enhances normally while the other 3 conditions enhances less than the normal pancreas in the arterial phase. Diffuse pancreatic ductal carcinoma and autoimmune pancreatitis can exhibit a rim while Mahvash disease and diffuse lymphoma don't. Peripancreatic vascular involvement and lymphadenopathy are usually not present in Mahvash disease but exist to various degrees in the others. Finally, Mahvash disease, diffuse pancreatic ductal adenocarcinoma, and diffuse pancreatic lymphoma usually don't have extra-pancreatic manifestations while autoimmune pancreatitis often is associated with lesions in many other organs[12-14].

Although Mahvash disease is rare, it can be readily singled out if the unique imaging features of Mahvash disease are appreciated. In a recent series of 245 cases of diffuse pancreatic enlargement, 55% of cases were due to autoimmune pancreatitis, 36% were due to diffuse pancreatic ductal carcinoma, 2% were due to diffuse pancreatic lymphoma, and 5% were due to diffuse pancreatic neuroendocrine tumors[15]. I wrote a letter to the journal where this series was published and suggested that Mahvash disease can be present among the patients with diffuse pancreatic neuroendocrine tumors. Lo and behold, the authors of the series subsequently identified a case of Mahvash disease in their series, which is the first case of Mahvash disease in their home country and is caused by novel glucagon receptor mutations[16]. Thus 1 in

Table 1 Comparison of pancreas imaging features of Mahvash disease, diffuse pancreatic ductal carcinoma, diffuse pancreatic lymphoma, and autoimmune pancreatitis

Pancreas imaging features	Mahvash disease	Diffuse pancreatic ductal carcinoma	Diffuse pancreatic lymphoma	Autoimmune pancreatitis
Pancreatic size	Moderately to enormously enlarged	Slightly enlarged	Moderately enlarged	Moderately enlarged
Pancreas contour	Preserved	Lost (sausage-shaped)	Lost (sausage-shaped)	Lost (sausage-shaped)
Pancreas parenchyma	Normal	Hypo enhancing relative to normal pancreas	Hypo enhancing relative to normal pancreas	Hypo enhancing relative to normal pancreas
Pancreatic rim	No	Enhancing rim in some patients	No	Hypo enhancing rim
Pancreatic mass	None or single or multiple lesions	No	No	None or single or multiple enhancing lesions
Vascular involvement	No	Yes	Yes	Yes
Lymphadenopathy	No	Yes in some patients	Yes	Yes
Extra pancreatic organs involvement	No	No	No	Yes

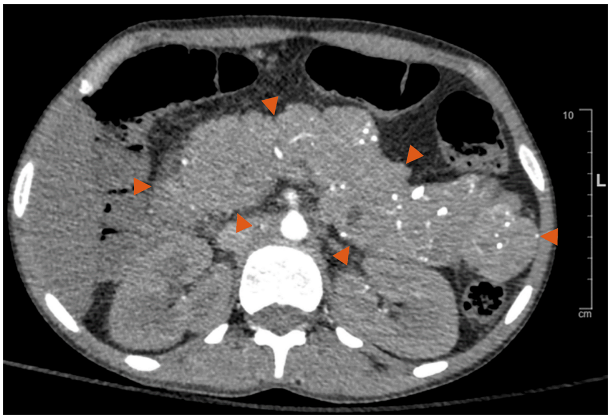

Figure 1 Pancreas in Mahvash disease, axial view of computed tomography with enhancement. Note the enormously and evenly enlarged pancreas with normal pancreatic contour. Also note the multiple punctate calcifications in the pancreas.

245 cases of diffuse pancreatic enlargement can be caused by Mahvash disease. The yield of identifying Mahvash disease will be much higher after radiologists integrate the nuanced imagining features of Mahvash disease, diffuse pancreatic ductal carcinoma, diffuse pancreatic lymphoma, and autoimmune pancreatitis.

In summary, Mahvash disease is a potentially lethal, autosomal recessive hereditary disease of pancreatic neuroendocrine tumors and inborn error of metabolism. The diagnosis of Mahvash disease has been delayed in the past largely due to radiologists' unawareness of or unfamiliarity with the unique imaging features of Mahvash disease. On the other hand, a recent example shows that Mahvash disease can be readily diagnosed once its imaging features are appreciated. To prevent missing the diagnosis of this remarkable disease, I make a plea to radiologists to please consider Mahvash disease in their differential diagnoses of diffusely enlarged pancreas.

FOOTNOTES

Author contributions: Yu R wrote the paper.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

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S-Editor: Fan M
L-Editor: A
P-Editor: Chen YX

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