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Gastrointestinal Imaging

Acute Pancreatic Transplant Rejection: Evaluation with Dynamic Contrast-enhanced MR Imaging Compared with Histopathologic Analysis

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Abstract

PURPOSE: To evaluate the use of dynamic contrast material-enhanced gradient-recalled-echo MR imaging for the diagnosis of acute pancreatic transplant rejection, as confirmed at histopathologic analysis.

MATERIALS AND METHODS: Thirty MR imaging studies were performed in 25 patients within 3 days of percutaneous biopsy or pancreatectomy. The mean percentage of parenchymal enhancement (MPPE) at dynamic contrast-enhanced MR imaging was calculated.

RESULTS: Biopsy findings were no evidence of rejection ($n = 7$ [23%]), mild rejection ($n = 10$ [33%]), moderate ($n = 6$ [20%]) and severe ($n = 2$ [7%]) acute rejection, and infarction ($n = 5$ [17%]). The corresponding MPPEs at 1 minute were 106%, 66%, 62%, 57%, and 3%, respectively. Overlap of cases in the normal and rejection groups occurred; however, using an MPPE cutoff of 100% resulted in a sensitivity of 96%. An MPPE over 120% was seen in the normal group only. The MPPE was significantly greater in the normal group than in the rejection or infarction group ($P < .05$).

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CONCLUSION: Dynamic contrast-enhanced MR imaging is highly sensitive for the detection of acute pancreatic transplant rejection. Because of overlap of cases in the normal and rejection groups, percutaneous biopsy may be needed in some cases. Pancreatic allografts with infarction can be clearly identified.

Index terms: Magnetic resonance (MR), contrast enhancement, 77.121412, 77.12143 • Magnetic resonance (MR), tissue characterization, 77.121412, 77.12143 • Pancreas, MR, 77.121412, 77.12143, 77.12144, 77.12146 • Pancreas, transplantation, 77.458

Introduction

Pancreatic transplantation is performed in selected patients who have major complications of type 1 diabetes mellitus. Advances in surgical technique and postoperative management have improved graft survival; however, up to 60% of pancreatic transplants have rejection episodes (1). Early detection of acute rejection is required to institute antirejection therapy promptly and avert graft loss. Clinical and biochemical indicators of rejection have proved to be relatively insensitive and nonspecific in determining acute rejection (2,3). Similarly, computed tomography (CT) and ultrasonography (US) have been demonstrated to be unreliable for the detection of acute rejection (4–6).

Spin-echo MR imaging and gadopentetate dimeglumine-enhanced MR imaging have been inconsistent in the evaluation of pancreatic transplant dysfunction (7–9). In these series, only a few cases were correlated with histopathologic results; most of the acute rejection cases were diagnosed by using clinical or biochemical evaluation. Few pancreatic biopsy procedures were performed in prior studies because of the perceived risk of complications and the need for general anesthesia and open biopsy (10). Recent developments in percutaneous technique now enable safe and consistent biopsy of pancreatic transplants (5,11–14) and thereby enable standard-of-reference correlation with imaging findings. We analyzed the usefulness of dynamic contrast material-enhanced MR imaging in the diagnosis of acute rejection by correlating MR imaging enhancement patterns with histopathologic findings obtained at imaging-guided percutaneous core biopsy or surgical explantation.

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MATERIALS AND METHODS

Patient Population

A computerized database of patients who had undergone pancreatic transplant MR imaging during 37 months, for a total of 158 MR imaging examinations, was created. The results of 32 studies were correlated with histopathologic findings within 3 days of the MR imaging examination. Two MR imaging studies were eliminated because of severe physiologic motion artifact, technical problems, or both; this resulted in a final study group of 30 images obtained in 25 patients (15 men, 10 women; mean age, 37 years; range 28–61 years). Fifteen patients had simultaneously transplanted pancreas and kidney allografts from the same donor (simultaneous pancreatic/kidney), and eight had unrelated donor pancreatic implants after a previously successful kidney transplant (pancreas after kidney). Two patients had a pancreatic transplant alone. Four studies were performed within 2 weeks after transplantation, with a mean time of study after surgery of 3.8 months (range, 5 days to 1.7 years). Patients were referred for MR imaging because of abnormal laboratory assay results that suggested allograft dysfunction in 24 cases and abdominal pain in six cases. No asymptomatic patients were studied.

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66%, 62%, 57%, and 3% in the transplanted organs with mild, moderate, and severe grades of rejection and with infarction, respectively (Fig 2). The MPPE in the normal group was significantly greater than that in the rejection subgroups ($P < .05$); however, there was an overlap of cases between these groups. Clear separation of the normal group and group with infarction ($P < .01$) was present without overlap. Pairwise analyses revealed no significant difference in MPPE between the different grades of rejection ($P > .05$), but there was significantly greater enhancement on the images in the rejection group than on those in the infarction group, without overlap ($P < .005$).

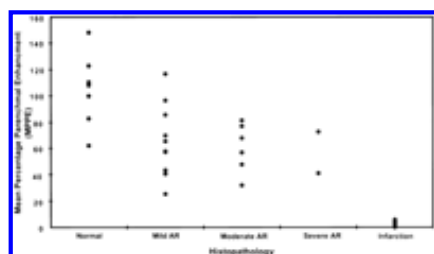


Figure 2. Scatter diagram shows the range of MPPEs at 1 minute with histopathologic diagnoses of normal, mild, moderate, and severe acute rejection and of infarction.

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If an MPPE cutoff value of 100% were used to predict rejection, a sensitivity, specificity, and accuracy of 96%, 67% and 87%, respectively, would result. The one false-negative case demonstrated mild acute rejection at histopathologic analysis and had an MPPE of 116% at MR imaging. Two of the three false-positive cases were in the normal group; the other was a case of infarction without rejection. If an MPPE cutoff of 20% were used to evaluate for transplant infarction, the resultant sensitivity and specificity each would be 100%.

DISCUSSION

Several MR imaging techniques have been evaluated for the noninvasive determination of acute pancreatic transplant rejection. Prior studies (7-9,16,17) in which the use of unenhanced MR imaging for assessment of pancreatic rejection was evaluated have had variable results and limited histopathologic correlation. Yuh et al (16) found spin-echo MR imaging to be 100% sensitive and 76% specific for acute pancreatic graft rejection in a series of 44 studies, as determined by using clinical assessment only. The allograft edema that occurs with acute rejection was qualitatively identified when the glandular signal intensity was either less than the signal intensity of muscle on T1-weighted images or greater than or equal to the signal intensity of the bladder urine on T2-weighted images. Vahey et al (17) quantitatively evaluated pancreatic transplant signal intensity on 13 MR imaging studies in nine patients. They found that the mean calculated T2 of the seven transplants with rejection was substantially elevated compared with that of the allografts without rejection. However, seven studies—five with pancreatic tissue and two with renal tissue—had histologic correlation. In comparison, by using clinical assessment, Kelcz et al (8) and Fernandez et al (9) evaluated the quantitative measurement of pancreatic transplant signal intensity with spin-echo sequences and were not able to demonstrate signal intensity differences in pancreatic allograft dysfunction.

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Experience with contrast-enhanced MR imaging for assessment of pancreatic allograft rejection has been limited. Fernandez et al (9) obtained dynamic, single-section contrast-enhanced MR images through the pancreatic transplant

during breath holding. They demonstrated that the percentage of enhancement in normally functioning pancreatic transplants was greater than that in dysfunctional allografts (with either rejection or infarction). In six cases of normally functioning allografts, they recorded a mean percentage of enhancement at 1 minute of 98% compared with 42% in six cases with acute dysfunction. In their series, the findings of five MR imaging studies were correlated with pancreatic transplant biopsy results.

Although many transplantation centers now use percutaneous pancreatic transplant biopsy to reliably diagnose acute rejection ([11,13,18](#)), this previously was not the case. Acute pancreatic rejection was thought to occur synchronously with acute renal rejection in simultaneously transplanted pancreas and kidney allografts from the same donor, and pancreatic rejection was not thought to occur in isolation ([19](#)). Because renal rejection could easily be diagnosed by using serum creatinine levels and percutaneous renal biopsy, the accepted practice was to use renal rejection to determine pancreatic rejection ([19–22](#)). However, it has been demonstrated that episodes of acute rejection after simultaneous renal and pancreatic transplantation may be discordant—that is, may occur in one organ but not in the other—in 22%–47% of cases ([23,24](#)). A sensitive noninvasive imaging study would be preferable because it would enable the small but substantial (ie, up to 3%) risk of major complications after percutaneous pancreatic biopsy to be avoided ([5,14](#)).

In our study, we compared the results of dynamic breath-hold contrast-enhanced pancreatic allograft MR imaging with those of standard-of-reference histopathologic analysis. Normally functioning transplanted organs tended to enhance avidly with contrast material administration, whereas the transplanted organs with rejection enhanced less actively. At 1 minute, the percentage of enhancement in the normal group was substantially greater, 106%, compared with 50% in the dysfunctional group (ie, transplants with rejection and infarction); these results are similar to those of the study by Fernandez et al ([9](#)). However, in their study, dysfunctional transplanted organs were not separated into rejection versus infarction groups, presumably because of the limited number of cases. In our study, the MPPE in the transplanted organs with rejection at 1 minute (63%) was markedly different from that in the transplanted organs with infarction (3%).

One of the mechanisms of dysfunction that occurs with acute pancreatic rejection is an alloimmune vasculitis ([25](#)). Decreased contrast enhancement in the transplanted organ, as occurred in the allografts with acute rejection in our study, may be due to narrowed or occluded small vessels, which result in a decreased rate and degree of accumulation of extracellular contrast material. For this purpose, gadolinium-based extracellular contrast materials for MR imaging have an advantage over the iodinated contrast materials that are used for CT, because most recipients have a coexistent renal transplant, and there is a reduced risk of nephrotoxicity.

The difference in enhancement between normal transplanted organs and dysfunctional allografts on gadolinium-enhanced GRE MR images may be useful in the clinical assessment and treatment of allograft recipients and in helping to guide the selective use of biopsy. In our study, despite the overlap of MPPE data points in the normal and rejection groups, the MPPE in the normal group was significantly different from that in the rejection group ($P < .05$). Gadolinium-enhanced GRE MR imaging appears to be highly sensitive for the detection of rejection; an MPPE cutoff of 100% resulted in a sensitivity of 96% ([Figs 3, 4](#)). In our series, the one false-negative case was due to infarction in a transplanted organ without acute rejection. Failure to diagnose this case by using MR imaging was not clinically relevant, because the allograft needed to be removed regardless of whether acute rejection was present. The two histopathologically normal false-positive cases, which occurred in transplanted organs that had diminished enhancement, were more problematic. If MR imaging had been used as the sole guide for antirejection treatment instead of biopsy, unnecessary therapy may have been instituted. These allografts may have had areas of acute rejection that were not detected because of biopsy sampling error. An MPPE of greater than 120% was demonstrated in normally functioning allografts only; this indicates that this group may not require biopsy. There was a very small number of such cases in our series. The converse may also be useful; allografts with an MPPE of less than 60% were dysfunctional owing to either acute rejection or infarction.

Another reason to develop a clinically useful imaging technique for the diagnosis of acute rejection in pancreatic allografts is that pancreatic allografts are no longer routinely placed in the pelvis (26). Instead, the pancreatic allograft is placed in the mesentery of the middle part of the abdomen, with portal venous drainage of endocrine secretions. Portal venous–drained pancreatic transplants have the theoretic advantage of normalized insulin physiology (26). Unfortunately, these transplanted organs are more difficult to monitor with imaging because they are often located deeply within the abdomen and may have surrounding interposed bowel; therefore, they are also more difficult to perform biopsy on percutaneously. Hence, a sensitive, noninvasive alternative for predicting rejection episodes has greater importance.

Graft thrombosis that leads to allograft infarction is another major cause of graft loss. This event can occur early (ie, in less than 1 month) or late after surgery. Early graft thrombosis, as occurred in one patient in this series, is usually the result of vascular graft anastomotic error or microvascular damage from preservation injury. Late thrombosis (ie, that which occurs more than a month after surgery), as occurred in four cases in this series, usually results from severe acute rejection with alloimmune arteritis and causes occlusion of small vessels, which leads to complete major vessel occlusion. Regardless of the causes, all cases with an MPPE of less than 10% in our study had infarction and were identified by using gadolinium-enhanced GRE MR imaging (Fig 5). Identification of total graft thrombosis and infarction is important, because the transplanted organ should be removed immediately to avoid the severe systemic effects of graft autolysis (21). Acute rejection, regardless of its severity, is usually treated medically, and the allograft usually does not need to be removed; however, it may be difficult to differentiate severe rejection from graft infarction in the clinical setting. In our study, there was no overlap of cases between the rejection subgroups and the infarction group. Therefore, the described technique appears to be useful in separating these two diagnoses. This supports the findings in previous MR imaging literature (27), which have demonstrated a lack of enhancement in pancreatic allografts with infarction in a small number of cases.

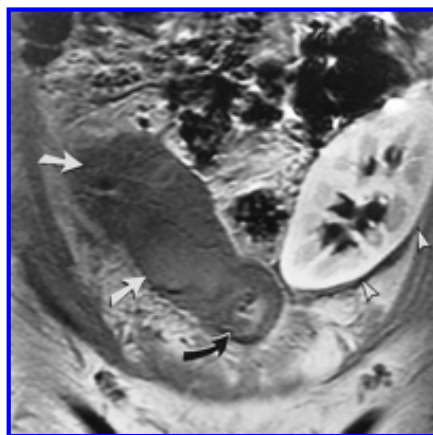


Figure 5. Coronal fast multiplanar spoiled GRE MR image (150/4.2, 60° flip angle) obtained 1 minute after the administration of gadolinium-based contrast material in a patient with pancreatic allograft infarction that was proved at surgical explantation. There is no enhancement in the enlarged pancreatic allograft (white arrows) or in the duodenal cuff (black arrow). The measured MPPE was 1%. A normal enhancing renal transplant (arrowheads) is noted.

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Limitations of this study include a relatively small patient population. At our institution, MR imaging is used for problematic cases that could not be adequately assessed by using US or CT. The study group was further diminished because of our requirement that a maximum of 3 days intervene between the histopathologic and MR imaging examinations (mean interval, 1.4 days). Increasing this interval would have increased the number of cases in the series, but it would have diminished the quality of the histopathologic correlation. A further limitation of our study is that percutaneous biopsy was performed on only one site in the pancreas allograft. We could have potentially underdiagnosed the prevalence of acute rejection. In addition, because the study was performed retrospectively, the use of the described

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