Imaging of Tropical Chronic Pancreatitis—A Unique Clinico-Radiological Entity

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Tropical chronic pancreatitis (TCP) is a unique juvenile nonalcoholic form of chronic pancreatitis prevalent in tropical developing countries. TCP is characterized by the younger age of onset, rapid progression, higher prevalence of diabetes and pancreatic calculi, and greater propensity to develop pancreatic malignancy. Identifying the distinct imaging features is critical for the diagnosis of TCP. Awareness of this condition will not only enable the radiologist to recognize it early but also help in better management. In this article, we review the etiopathogenesis, distinct imaging features, and complications of TCP.

Abstract

Keywords
► chronic calcific pancreatitis
► tropical pancreatitis
► mutation
► computed tomography
► magnetic resonance imaging
► pancreatic malignancy

Introduction

Tropical chronic pancreatitis (TCP) is a unique juvenile nonalcoholic form of chronic pancreatitis prevalent in tropical developing countries. TCP is characterized by the younger age of onset, rapid progression, higher prevalence of diabetes and pancreatic calculi, and higher propensity to develop pancreatic malignancy. The usual clinical scenario of TCP can be witnessed in a child, adolescent or young adult presented with recurrent attacks of abdominal pain, steatorrhea, and diabetes which usually sets in by the third decade. The diabetic stage of the disease is referred to as fibrocalculous pancreatic diabetes. The diabetes is severe and requires high doses of insulin although ketosis is uncommon. Demonstration of high blood sugar level and pancreatic calculi on imaging confirms the diagnosis.² Zuidema from Indonesia was the first to describe a series of 45 cases of TCP.³ Geevarghese et al reported the largest series of TCP in the world from the south-western Indian state of Kerala.⁴ The prevalence of chronic pancreatitis in the Western population is 10 to 15 per 100,000, which is considerably lesser compared with the prevalence of 120 to 200 per 100,000 in certain parts of south India.¹ TCP is unique compared with other forms of chronic pancreatitis in its etiology, imaging features, and prognosis. In this article, we review the etiopathogenesis and distinct imaging features and complications of TCP.

Etio-Pathogenesis

Malnutrition, consumption of cassava, viral infection, and familial and genetic factors have been implicated in the causation of TCP. The main mechanism of pancreatic damage (acinar cell injury) is autodigestion by trypsin. Mutations in genes that prevent premature activation of trypsinogen to trypsin lead to as fibrocalculous pancreatic diabetes. The diabetes is severe and requires high doses of insulin although ketosis is uncommon. Demonstration of high blood sugar level and pancreatic calculi on imaging confirms the diagnosis.¹ Zuidema from Indonesia was the first to describe a series of 45 cases of TCP.³ Geevarghese et al reported the largest series of TCP in the world from the south-western Indian state of Kerala.⁴ The prevalence of chronic pancreatitis in the Western population is 10 to 15 per 100,000, which is considerably lesser compared with the prevalence of 120 to 200 per 100,000 in certain parts of south India.¹ TCP is unique compared with other forms of chronic pancreatitis in its etiology, imaging features, and prognosis. In this article, we review the etiopathogenesis and distinct imaging features and complications of TCP.

Etio-Pathogenesis

Malnutrition, consumption of cassava, viral infection, and familial and genetic factors have been implicated in the causation of TCP. The main mechanism of pancreatic damage (acinar cell injury) is autodigestion by trypsin. Mutations in genes that prevent premature activation of trypsinogen to trypsin lead to pancreaticitis. Mutations with high prevalence in TCP are serine protease inhibitor (SPINK 1), cationic trypsinogen gene (PRSS 1), and cystic fibrosis transmembrane conductance regulator (CFTR) gene. A recent study from India showed a high association of tropical pancreatitis with SPINK N34S mutation. These mutations are believed to lead toward
sentinel pancreatitis, and combined with other exogenous factors precipitate further recurrent episodes of pancreatitis in predisposed patients (Fig. 1).

Pathology
The morphological features of pancreas depend on the duration and severity of the disease. Parenchymal atrophy is variable and the size of gland is inversely proportional to duration. Fibrosis is the most important microscopic finding and also the main cause of atrophy of the gland. In advanced stages, the gland is replaced by adipose tissue. The pancreatic ducts show areas of stenosis and dilatation. The characteristic intraductal calculi of varying size (millimetric to 5 cm) are observed. The core organic matrix of calculi consists of desquamated epithelium, fibrin, mucin, and protein deposits. Later, calcium (predominantly in form of calcium carbonate) deposits in the periphery of this matrix.

The characteristic microscopic finding in TCP is the peri-ductular fibrosis, predominantly involving the main duct and small ductules leading to marked dilatation of the ducts. Immunohistochemistry has shown an overall decrease in the percent of α cells and β cells. The decrease in insulin positivity in the islets is often inversely proportional to the duration of diabetes.

Imaging
Imaging and diagnosis of TCP are almost never made in the early stages, as the dominant symptom of abdominal pain is non-specific. The imaging feature depends on the stage of the disease. In the early stages, small calculi can be detected only on computed tomography (CT) or ultrasound and can be easily missed on plain radiographs. Ultrasound is a useful tool to regularly follow up these patients and to detect complications. When the pancreatic parenchyma is completely replaced by the fat, the echogenic fat on an ultrasound could mimic the normal pancreas. CT is the modality of choice, as it allows complete visualization of the gland, detection of calcifications, and identification of associated complications. As the onset of TCP is at a younger age, these patients require frequent imaging for early detection of the complications/neoplasm. Although CT is a sensitive tool, the cumulative radiation dose is a cause for concern. Magnetic Resonance Imaging (MRI) is an excellent modality to delineate the ductal anatomy and conduct follow-up imaging of younger patients. However, when the ducts are packed with the calculi, visualization of the ducts on magnetic resonance cholangiopancreatography (MRCP) is compromised.

Pancreatic Parenchyma and Pancreatic Duct
Pancreatic size is inversely proportional to the duration of the disease. The degree of duct dilatation also increases as the disease progresses. Diffuse and massive main ductal dilatation is a common pattern. However, focal dilatation involving either head, body, or tail region can also be observed.

Pancreatic Calculi
Identifying the characteristic distribution of calculi is a crucial factor in establishing the diagnosis of TCP. The stones range in size from small sand-like particles to 5 cm. Usually, the stones in the head region are larger and denser, whereas size and density progressively decrease toward the tail region. The shape of calculi depends on location and may be smooth elongated, rounded, or staghorn shape. Various distribution patterns can be identified in TCP. The most common and characteristic
Fig. 2 An 18-year-old male patient with tropical chronic pancreatitis (TCP) and diabetes mellitus. Contrast CT axial images (A, B). Ultrasound images (C, D) show pancreatic parenchyma completely replaced by fat (B, arrow). Echogenic fat on ultrasound can mimic normal pancreas (D, arrow). Note the dilated main pancreatic duct (MPD) with intraductal calculi (A, C arrow).

Fig. 3 A 20-year-old male patient with tropical chronic pancreatitis (TCP) and diabetes mellitus. Contrast CT axial images (A), T2 weighted MR axial image (B), MRCP image (C) show dilated main pancreatic duct (MPD) packed with the calculi (A, arrow). Packed intraductal calculi cause difficulty in the visualization of the pancreatic duct on MRI (B, arrow) and MRCP (C, arrow) images.

Fig. 4 A 25-year-old male patient with tropical chronic pancreatitis (TCP) and diabetes mellitus. Axial images (A, B) of contrast CT shows completely atrophic pancreas (not visualized), hugely dilated main pancreatic duct (A, arrow) and large intraductal calculi in the head region of the pancreas (B, arrow). Note absence of calculi in the body and tail region.
pattern is diffusely scattered large intraductal calculi throughout the head, body, and tail region (►Fig. 5). The second pattern is large calculi distributed predominantly in the head region of the pancreas (►Fig. 4). An uncommon pattern is numerous tiny calculi diffusely scattered throughout the gland. This pattern is indistinguishable from alcoholic calcific pancreatitis, which is the most common cause of chronic calcific pancreatitis worldwide. However, the calculi in alcoholic pancreatitis are fine, speckled and have hazy margins, while those in TCP are dense and discrete. The overlap of alcohol abuse in many patients with TCP can make clinical and radiological diagnosis challenging (►Table 1). Another mimicker of TCP is hereditary pancreatitis, which is a rare autosomal dominant disease occurring in children. The calculi in hereditary pancreatitis are similar to alcoholic pancreatitis however ductal dilatation and pancreatic atrophy is less in comparison to TCP.

Intraductal Papillary Mucinous Neoplasm (IPMN) of the pancreas can clinically present itself as chronic pancreatitis. Moreover, irregular ductal dilatation and intraductal mucin calcification in these patients can make it difficult to differentiate it from TCP by imaging. Demonstration of the presence of intraductal papillary nodules or intraductal mucin, projection of the papilla into the duodenal lumen by CT/MRI, and endoscopy helps differentiate IPMN from TCP.

Patients with hyperparathyroidism and hypercalcemia are at increased risk of developing pancreatitis. The mechanism may involve deposition of calcium within the pancreatic duct and excessive conversion of trypsinogen to trypsin catalyzed by calcium. Imaging findings are indistinguishable from alcoholic pancreatitis, showing small pancreatic calcification distributed throughout the pancreas. Lesser degree of ductal dilatation, atrophy of gland, and small size of calcifications help in differentiating it from TCP.

Usually, patients with TCP require insulin for diabetes control. In patients not responding to medical management, surgical management is indicated. Surgical procedures such as Puestow procedure (longitudinal pancreaticojejunostomy), Duval procedure (distal pancreaticojejunostomy), and subtotal pancreatectomy have shown good results.

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<th>Tropical pancreatitis</th>
<th>Alcoholic pancreatitis</th>
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<tr>
<td>Geographic distribution</td>
<td>Tropical</td>
<td>Temperate</td>
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<tr>
<td>Age of onset</td>
<td>Young</td>
<td>Middle age</td>
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<tr>
<td>Cassava</td>
<td>High intake</td>
<td>No intake</td>
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<td>Nutrition</td>
<td>Mal-nourished</td>
<td>Well-nourished</td>
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<td>Alcoholism</td>
<td>Non-alcoholics</td>
<td>Alcoholics</td>
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<tr>
<td>Diabetes</td>
<td>70 to 80%, before or with the onset of pain. Severe, insulin-dependent but ketosis resistant</td>
<td>50%, after the onset of pain. Mild diabetes</td>
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<td>Pancreatic duct</td>
<td>Markedly dilated</td>
<td>Less dilated</td>
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<td>Calculi</td>
<td>Dense, large, discrete, always large duct, seldom parenchymal</td>
<td>Fine, speckled, hazy margins, Parenchymal or small ducts Rarely large duct</td>
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<td>Course of disease</td>
<td>Rapid progression</td>
<td>Slow progression</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Common</td>
<td>Less common</td>
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deaths in TCP are due to complications secondary to diabetes. Other causes of mortality are severe infections, pancreatic cancer, and pancreatitis-related complications.41

Complications

Acute on Chronic Pancreatitis

Patients with TCP have recurrent episodes of acute exacerbations. CT is a useful modality to detect early changes. The gland shows focal or diffuse enlargement in the background of CCP. Increased density in the peripancreatic fat, thickening of fascial planes, and fluid collection (intra-pancreatic, peri-pancreatic space, and lesser sac) indicates acute exacerbation of the disease (►Fig. 6).42

Pseudocysts

Evolution of fluid collection into pseudocyst occurs over a period between 4 and 6 weeks. Pseudocysts are composed of a thick, well-defined capsule of dense fibrous connective tissue (►Fig. 7). Larger pseudocysts (>5 cm) usually do not undergo spontaneous resolution and require intervention. Usually, pseudocysts possess water density attenuation content. Increase in the density of pseudocyst content may be secondary to infection or hemorrhage (hemosucchus pancreaticus). Although CT characterizes the collections/pseudocysts, sometimes MRI/MRCP could be helpful in delineating the ductal communication with the pseudocysts.43

Biliary Obstruction

Biliary obstruction can be secondary to benign distal common bile duct (CBD) strictures or pancreatic head malignancy. Benign strictures show a smooth narrowing of distal CBD with low grade intrahepatic biliary dilatation, whereas pancreatic head malignancy causes abrupt cut off of distal CBD with high grade intrahepatic biliary dilatation (►Fig. 8).44,45

Vascular Complications

The incidence of pseudoaneurysm of visceral arteries in chronic pancreatitis is 7 to 10%, greater than in acute pancreatitis (1–6%).46,47 Various mechanisms of pseudoaneurysm formation are as follows: enzymatic autodigestion of arterial wall leading to pseudoaneurysm formation, visceral artery eroding into pseudocyst converting pseudocyst into a pseudoaneurysm, and pseudocyst eroding into bowel wall with bleeding from the mucosal surface (►Fig. 9). TCP frequently causes thrombosis of the splenic vein.46,48 Multiphase CT detects the site and cause of the bleed with good sensitivity. It also provides a good vascular roadmap for surgery or embolization.49,50

Malignant versus Inflammatory Masses

Various studies have shown that 7 to 10% of patients with TCP develop pancreatic carcinoma. Compared with other forms of chronic pancreatitis, malignancy complicating TCP occurs at a much younger age and has a worse prognosis. TCP patients have a hundredfold increased risk of developing pancreatic cancer than controls.50,51 A common problem faced in imaging of patients with TCP is to differentiate between the inflammatory mass (pseudotumor) and the pancreatic carcinoma. The shrunken and atrophic pancreas is the most frequent finding in TCP. However, the focal inflammatory process may mimic carcinoma (►Fig. 8).52–54 With advances in CT and MRI, various investigators have attempted to differentiate inflammatory mass from carcinoma. Studies show that both inflammatory mass and carcinoma histologically consist of abundant fibrosis, and show hypoenhancement

Fig. 6 A 30-year-old male patient with tropical chronic pancreatitis (TCP) presented with acute pain abdomen. Axial plain images (A–C) and axial contrast images (D–F) of Computed tomography (CT) show atrophic pancreas and uniform sized large intraductal calculi distributed throughout the pancreas (A–G arrow). Bulky head of the pancreas (D, arrowhead) with surrounding fat stranding (E, arrowhead) suggestive of acute on chronic pancreatitis.
Fig. 7 A 35-year-old male patient with tropical chronic pancreatitis (TCP) with a recurrent episode of acute pancreatitis. Axial contrast CT images show atrophic pancreas, dilated main pancreatic duct (C, arrow), large intraductal calculi in the head (A, arrow), body region (B, arrow) and pseudocyst in the body region of the pancreas (C, arrowhead).

Fig. 8 A 39-year-old male patient with tropical chronic pancreatitis (TCP) with a recurrent episode of acute pancreatitis. Axial (A–C) and coronal (D, E) Contrast CT images show irregular dilated main pancreatic duct (A, arrow) and calcifications in the head region (C, arrow). A hypodense mass in the head region (B, D arrow) causing smooth narrowing of distal CBD (E, arrow) with no significant biliary obstruction. EUS guided biopsy done from head mass and histopathology report was non-malignant inflammatory mass.
in contrast-enhanced CT or MRI images. Johnson PT et al observed that masses, due to chronic pancreatitis and pancreatic carcinoma, show delayed progressive enhancement on dynamic contrast MRI and attributed this to the abundant fibrosis within these masses.55 Kumaresan S et al studied the utility of diffusion-weighted imaging (DWI) in differentiating inflammatory mass from carcinoma and concluded that DWI does not add any additional value with regard to differentiating between the two.56 Secondary signs which can point toward malignancy are metastases, the abrupt cutoff of CBD, and vascular invasion (►Fig. 10).44,45 Any soft tissue appearing in a completely atrophic gland on follow-up imaging should be treated with high suspicion. Although endoscopic ultrasound (EUS) has high resolution, studies have shown its limited role in differentiating inflammatory mass from carcinoma. EUS provides good guidance for fine needle aspiration (FNA) or biopsy. However, the sensitivity of EUS-FNA for malignancy in parenchymal masses with features of TCP is low (54–74%).57–61 The only reliable method of confirming malignancy is histopathology of the surgical specimen.

### Changing Trends in TCP

Balakrishna et al have extensively studied TCP over a period of 30 years and have observed the changing trends in the TCP. The disease now occurs in older individuals, who have milder diabetes which can be controlled using oral hypoglycemic agents. TCP is now a more heterogeneous disease, sometimes presenting itself in classical form and often resembling idiopathic or alcoholic chronic pancreatitis. In a particular patient, more than one etiological factor may be operating in tandem and their relative contributions determine the manifestations of TCP.1

### Conclusion

TCP is a unique, rapidly progressing calcific pancreatitis occurring among younger non-alcoholic patients. It has a higher propensity to develop malignancy at a younger age with a worse prognosis. TCP is also showing a change in pattern, with cases reported from the temperate region and from those afflicted with milder diabetes. The typical

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**Fig. 9** A 32-year-old male patient with tropical chronic pancreatitis (TCP) with haematemesis. Contrast CT (A) and DSA (B, C) images show calcifications in the head region (A, arrowhead) and pseudoaneurysm from gastroduodenal artery branch (A, yellow arrow; B arrow). Isolation of pseudoaneurysm achieved by coil trapping technique (C, arrow).

**Fig. 10** A 38-year-old female patient with tropical chronic pancreatitis (TCP). Axial (A–C) and coronal (D–F) Contrast CT images show, atrophic pancreas, dilated main pancreatic duct (MPD) (A, arrowhead) with multiple intraductal calculi (A, D arrow). An irregular hypodense mass (B, arrow) in pancreatic body region with encasement and narrowing of celiac artery (C, arrow), hepatic artery (E, arrowhead), SMA (F, arrow) and occlusion of main portal vein (E, arrow) with multiple collaterals at hilum (D, arrowhead). Histopathology report was adenocarcinoma.
imaging features of this condition helps in differentiating it from other forms of calcific pancreatitis. Awareness of this unique pathogenetic entity will enable the radiologist to recognize it early. Intervention at an early stage, using newer therapeutic approaches, could help to ensure better survival and prognosis. Population-wide genetic studies could help in the prevention of this condition in the future.

Conflict of Interest
None declared.

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