Check for updates

Received: 12 August 2024 | Revised: 29 August 2024 | Accepted: 4 September 2024

DOI: 10.1002/jcu.23823

WILEY

CASE REPORT

TRPV6 gene mutation associated with giant pancreatic pseudocyst with mediastinal extension in a pediatric patient: Lessons learned

Seda Nur Tosun[1] | Merve Yazol[1] | Sümeyye Ballıtaş[1] | Zafer Türkyılmaz[2] | Öznur Leman Boyunaga[1]

[1]Department of Radiology, Gazi University School of Medicine, Ankara, Turkey

[2]Department of Pediatric Surgery, Gazi University School of Medicine, Ankara, Turkey

Correspondence
Seda Nur Tosun, Department of Radiology, Gazi University School of Medicine, Ankara 06560, Turkey.
Email: sedanurg9431@gmail.com

Abstract

Pancreatic pseudocyst is a common complication secondary to acute or chronic pancreatitis. The extension of a pseudocyst into the mediastinum is extremely rare, with notably few reported cases in the pediatric age group found in the literature. This report presents a giant pancreatic pseudocyst with mediastinal extension that developed secondary to TRPV6 gene mutation in a 12-year-old male patient with no previously known disease and normal laboratory values.

KEYWORDS
chronic pancreatitis, mediastinal extension, pediatric, pseudocyst, TRPV6 gene

1 | INTRODUCTION

Pancreatic pseudocysts are localized fluid collections without an epithelial lining. Pathophysiologically, they are formed after extravasation of pancreatic enzymes due to injury of the main pancreatic duct or its branches. These pseudocysts typically develop within 4–6 weeks after the initial pancreatic injury.[1] Pseudocysts vary widely in size, number, and location. A "giant pseudocyst" is defined as a pseudocyst with a maximum diameter of 10 cm or greater.[2] Since pseudocyst formation is a complication of pancreatitis, the etiology of both conditions is the same.[1]

While pancreatitis is mainly seen secondary to alcohol use in adult patients, the most common cause in pediatric patients is blunt abdominal trauma.[3] Pancreatic pseudocysts with mediastinal extension are rare; they develop by leakage of pancreatic secretions into the mediastinum through the diaphragmatic spaces, usually from the esophageal or aortic hiatus.[4] The first description of a pancreatic pseudocyst with mediastinal extension in pediatric patients was provided by Galligan and Williams in 1966.[5] According to our literature review, up to 2023, there have been only 15 reported cases besides ours.[6] This article presents the diagnosis and treatment of pancreatic pseudocyst extending to the mediastinum in a 12-year-old male patient with no known disease secondary to TRPV6 gene mutation.

2 | CASE REPORT

A 12-year-old male patient was initially seen in a local hospital with complaints of exertional dyspnea and cyanosis, loss of appetite, and weight loss for approximately 1.5 months. A non-contrast chest computed tomography (CT) scan identified a large retrocardiac cystic lesion. He was referred to our department with a preliminary diagnosis of teratoma.

At the time of hospitalization, the patient's weight was 35 kg (10th–25th percentile), height was 150 cm (50th percentile), and the body-mass index was 15.6 kg/m^2 (within the normal range), and there was no reported family history of chronic pancreatitis. However, he was born into a consanguineous marriage (between first cousins). Laboratory studies, including complete blood count, coagulation profile, and liver function tests, were within the normal ranges.

A chest x-ray revealed a large radiopacity in the posterior mediastinum and abdomen, obscuring the medial border of the right diaphragm (Figure 1). An ultrasound (US) examination showed a large abdominal component of the cyst. Repeated contrast-enhanced CT examination of the chest and abdomen revealed a giant cystic lesion measuring 10×12×15 cm that extends to the pancreatic tail.

Left anterolateral displacement of the esophagus, compressive atelectasis in the adjacent lower lobe of the left lung, compression of the gastric cardia, and lesser curvature secondary to the cystic lesion

 © 2024 Wiley Periodicals LLC.

were noted (Figure 2A). These findings were accompanied by pleural effusion measuring 1 cm in the left hemithorax and minimal free fluid around the cyst in the subdiaphragmatic area. Furthermore, CT examination revealed atrophy and coarse calcification throughout the pancreas, dilation of the main pancreatic duct, and several millimeter-sized calcification foci in the main pancreatic duct (Figure 2B). No significant pathology was observed in the remaining abdominal and pelvic sections. The findings led to a consideration of chronic pancreatitis and a giant pancreatic pseudocyst with mediastinal extension for the diagnosis.

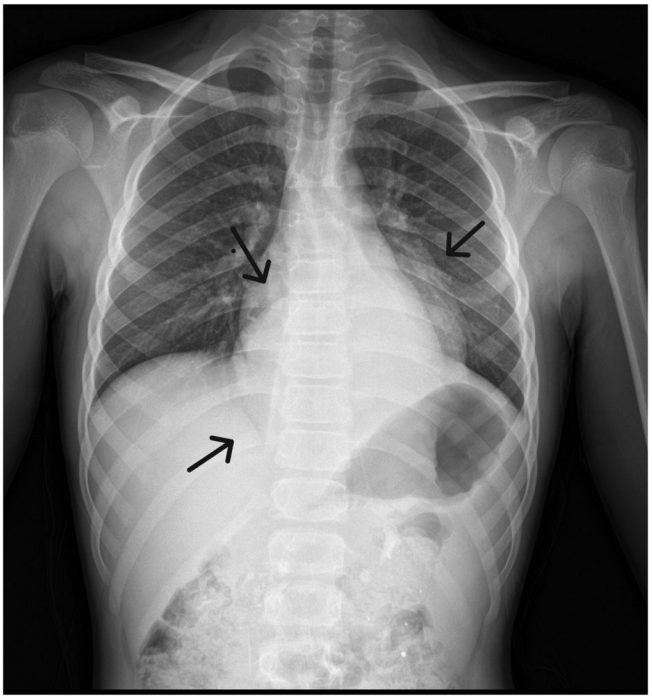


FIGURE 1 (A) Chest x-ray showing a large radiopacity localized in the mediastinum, retrocardiac area, and abdomen. An ultrasound (not shown) examination showed a large abdominal component of the cyst.

The interventional radiology department placed a US-guided percutaneous drainage catheter through a posterior approach. The catheter was removed after it was confirmed that no more fluid was being drained. While amylase and lipase values in the patient's serum were within the normal range, amylase (23 150 U/L) and lipase (23 020 U/L) values studied from the sample taken from the cyst during US guidance drainage were significantly higher in favor of pancreatic pseudocyst. Magnetic resonance cholangiopancreatography (MRCP) imaging performed 2 days post-drainage showed a significant decrease in the size of the mediastinal component of the cystic lesion, while no significant difference was found in the abdominal component. MRCP imaging also revealed a connection between the cystic lesion and the main pancreatic duct (Figure 3).

Following the identification of pseudocyst and chronic pancreatitis, next-generation sequencing (NGS) was used to analyze the genes that have been linked to the etiology of chronic pancreatitis. DNA was extracted from the peripheral blood, and the results showed that our patient was heterozygous in terms of the TRPV6 (NM_018646.6) gene variant (c.268del).

Surgery was performed for the treatment of a residual pseudocyst measuring approximately 5.5×3.5 cm adjacent to the tail of the pancreas. The procedure involved removing stones from the main pancreatic duct and performing pancreaticojejunostomy and jejunojejunostomy. The patient was discharged on the 7th postoperative day with multivitamins and a modified diet.

At the 6-month post-procedure follow-up in the pediatric surgery outpatient clinic, the patient was asymptomatic. His weight had increased to 43 kg (25th percentile), his height to 155 cm (25th–50th percentile), and his body mass index to 17.9 kg/m^2 (within the normal range). The patient continues to be followed up regularly.

3 | DISCUSSION

A pseudocyst with mediastinal extension is exceedingly rare, especially in the pediatric population.[3] Pancreatic fluid extension into the

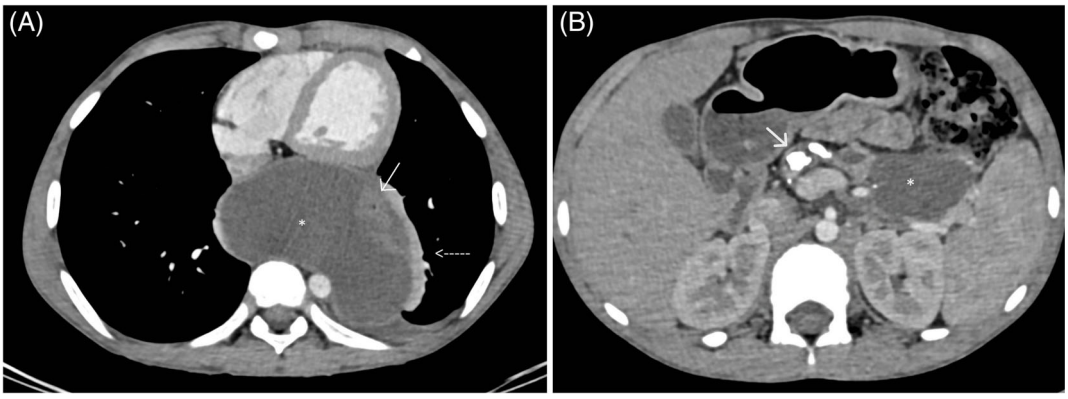


FIGURE 2 (A) An axial section of a contrast-enhanced computed tomography scan shows a large cystic lesion (asterisk) located in the posterior mediastinum, left anterolateral displacement of the esophagus (arrow) secondary to cyst compression, and compressive atelectasis (dashed arrow) in the segment of the left lung's lower lobe. (B) Atrophy of the pancreas accompanying the cystic lesion (asterisk) extending to the tail of the pancreas and foci of calcification within the main pancreatic duct (arrow).

10970096, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jcu.23823 by Merve Yazol - Macquarie University , Wiley Online Library on [12/09/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

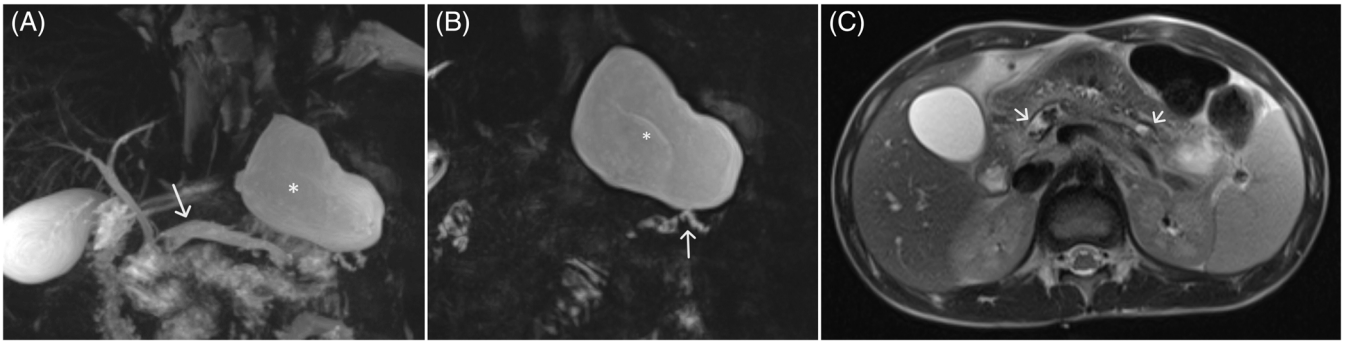


FIGURE 3 (A) Dilation of the main pancreatic duct (arrow) with the abdominal persisting component of pseudocyst (asterisk) on magnetic resonance cholangiopancreatography (MRCP) examination. (B) Relationship (arrow) between the distal part of the main pancreatic duct and pseudocyst (asterisk) on MRCP examination. (C) Main pancreatic duct dilation on T2A axial section (arrows) and hypointense filling defects compatible with intraluminal stones.

posterior mediastinum occurs through the esophageal or aortic hiatus in the majority of these cases. In some rare cases of extension through the foramen Morgagni, pseudocysts are localized in the middle or anterior mediastinum.[1,4,7]

Unlike in adult patients, the causes of chronic pancreatitis in pediatric patients include idiopathic and autoimmune pancreatitis, hereditary pancreatitis, anatomical anomalies including pancreatic divisum, cystic fibrosis, and metabolic diseases including hyperlipidemia and hyperparathyroidism. Mutations of genes including cationic trypsinogen gene (PRSS1 or PRSS2), serine protease inhibitor kazal type 1 (SPINK1), cystic fibrosis transmembrane conductance regulator (CFTR), chymotrypsin C (CTRC), and cathepsin B (CTSB) may be observed in the etiology of chronic pancreatitis.[8] Also, the transient receptor potential cation channel subfamily V member 6 (*TRPV6*) gene is recently discovered as a novel gene associated with early-onset nonalcoholic chronic pancreatitis. Hereditary and familial chronic pancreatitis patients show a higher frequency of functionally defective TRPV6 variations compared to idiopathic chronic pancreatitis patients.[9] Calcium plays a crucial role in the etiology of pancreatitis. While the other genes linked to chronic pancreatitis affect the pancreatic digesting enzyme/enzyme inhibitor system, TRPV6 is crucial in maintaining calcium homeostasis, distinguishing it in the etiology of chronic pancreatitis.[10]

The clinical features of pseudocysts with mediastinal extension are quite nonspecific and usually develop due to compression of adjoining structures. Abdominal pain, nausea, vomiting, chest pain, dyspnea, and tachypnea can be observed.[3,4] Furthermore, life-threatening complications, including hemothorax, cardiac tamponade, acute airway obstruction, and esophagobronchial fistula, may also develop in pseudocysts.[11]

Chronic pancreatitis is a progressive inflammatory destruction of the pancreatic tissue, leading to exocrine and endocrine dysfunction. Serum amylase and lipase are often used for the diagnosis of acute pancreatitis, but in chronic pancreatitis, amylase and lipase levels may decrease according to the damage degree of the pancreatic tissue.[12] Thus, serum tests offered limited diagnostic value in chronic pancreatitis. Amylase and lipase values are often elevated; however, they may also be within normal limits, as in our case.[13]

Since clinical and laboratory features may be nonspecific, radiologic imaging is crucial in diagnosing. Although chest x-rays are not diagnostic, they can reveal pseudocysts as well-defined opacities in the mediastinum and provide information on accompanying pleural or pericardial effusions.[7] Sonographically, the appearance of the pseudocyst can vary over time. In earlier periods, pseudocysts tended to be more complicated, containing varying degrees of debris, whereas later, they became more homogenous with debris clearance. Although ultrasound is helpful in the diagnosis, it is insufficient compared to CT. Contrast-enhanced CT also provides information on other issues, such as pancreatic atrophy, calcifications, and dilation of the main pancreatic duct. However, CT scans have limitations, including their inability to differentiate between pseudocysts and some cystic masses, and the potential adverse effects of contrast media.[13]

Magnetic resonance imaging (MRI) and MRCP are valuable tools for detailed evaluation of the anatomy of the pancreatic duct and for showing the relationship between the pseudocyst and the pancreatic duct.[3] Although MRCP and endoscopic retrograde cholangiopancreatography (ERCP) offer similar sensitivity in imaging the pancreatic duct, MRCP holds the advantage of being non-invasive. Furthermore, the injection of contrast media during ERCP can lead to artificial distension of the pancreatic duct and its branches. Nonetheless, ERCP's advantage lies in its utility for treatment planning and execution. Endoscopic US (EUS) is another invasive method that can be used in diagnosis and treatment. Cyst aspiration can be performed with EUS, and the diagnosis can be confirmed, facilitating diagnosis confirmation through high amylase levels in the aspirated fluid or enabling differential diagnosis of the cystic mass lesion.[13]

Given the scarcity of cases in the literature, there are no established guidelines for treating pancreatic pseudocysts with mediastinal extension. Medical treatment mainly consists of bowel rest, total parenteral nutrition, and supportive therapy, including somatostatin analogs.[11]

Since 1a,25-dihydroxyvitamin D3 is known to control TRPV6 expression, the identification of TRPV6 as a novel gene for early-onset nonalcoholic chronic pancreatitis may have opened up a new avenue for therapeutic approaches. However, there hasn't been enough research, and further investigation is needed.[14] Invasive

10970096, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jcu.23823 by Merve Yazol - Macquarie University , Wiley Online Library on [12/09/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

treatment options for pseudocysts include percutaneous, endoscopic, or surgical methods. Percutaneous drainage, as demonstrated in our case, can be effectively guided by CT or ultrasound.[13] Endoscopic drainage procedures are gaining preference due to their less invasive nature compared to surgery. However, these methods are mainly reported in the adult population and require significant expertise.[1,6] Despite the emergence of less invasive alternatives, surgery remains the most common treatment for pancreatic pseudocysts with mediastinal extension. Open surgical procedures include pancreatic resection and internal or external drainage. The choice of surgical approach depends on the anatomic location of the cyst, with common procedures including cystogastrostomy, Roux-en-Y cystojejunostomy, and Puestow's procedure.[6,7]

The differential diagnosis of mediastinal cystic lesions includes bronchogenic cyst, duplication cyst, mediastinal neuroenteric cyst, pericardial cyst, lymphangioma, and pancreatic pseudocyst with mediastinal extension.[15]

This case is noteworthy due to the rarity of pancreatic pseudocysts with mediastinal extension in pediatric patients and the demonstration of a novel gene (TRPV6) associated with chronic pancreatitis in a patient with no known history of pancreatitis and normal laboratory values.

4 | CONCLUSIONS

Pancreatic pseudocyst with mediastinal extension is an extremely rare complication of pancreatitis, particularly in the pediatric population. Our case underscores the diagnostic challenges posed by this condition, as clinical and laboratory findings can be nonspecific. Consequently, radiologic imaging plays a pivotal role in diagnosis, and this entity should be included in the differential diagnosis of mediastinal cystic lesions. Notably, our case underscores the potential genetic basis of chronic pancreatitis and pseudocysts in pediatric patients, highlighted by the identification of the TRPV6 gene as a novel factor in early-onset nonalcoholic chronic pancreatitis. This discovery emphasizes the need to consider genetic mutations in the assessment and management of pediatric patients with suspected pancreatic pseudocysts or chronic pancreatitis.

FUNDING INFORMATION

No funding was received for this study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Not required by the institutional research ethics board for case reports.

CONSENT FOR PUBLICATION

Written informed consent for publication of their clinical details and clinical images was obtained from the parent of the patient.

ORCID

Seda Nur Tosun https://orcid.org/0000-0003-0569-1480
Merve Yazol https://orcid.org/0000-0003-1437-8998
Sümeyye Ballıtaş https://orcid.org/0009-0005-4306-7955
Zafer Türkyılmaz https://orcid.org/0000-0003-3464-9628
Öznur Leman Boyunaga https://orcid.org/0000-0002-5200-1588

REFERENCES

1. Misra D, Sood T. Pancreatic pseudocyst. 2020.
2. Nalwa HS, Lanka SP, Mederos R. Giant pseudocyst of the pancreas: a case report. *Cureus*. 2022;14(9):e29456.
3. Tewari S, Sushma A, Redkar R. Mediastinal extension of pancreatic pseudocyst: a rare pediatric presentation. *J Indian Assoc Pediatr Surg*. 2021;26(1):44-47.
4. Anand S, Dhua AK, Sharma K, Naranje P, Bhatnagar V. Mediastinal pancreatic pseudocyst in children: a case report and review of literature. *J Indian Assoc Pediatr Surg*. 2020;25(6):393-396.
5. Galligan JJ. Pancreatic pseudocysts in childhood. *Am J Dis Child*. 1966;112(5):479.
6. Pan Y et al. Mediastinal extension of a progressively enlarging pseudocyst treated by EUS-guided transgastric drainage in a child: a rare case report (with video). *Endoscopic Ultrasound*. 2023;12(1):135.
7. Kotb M, Oshiba A, Ashour K. Pseudopancreatic cyst extending into the mediastinum in a 7-year-old child. *Eur J Pediatr Surg Rep*. 2019;07(1):e24-e27.
8. Basu S, Bhatacharya M, das S, Debnath B, Sen S, Chatterjee A. Mediastinal pseudocyst and cardiac tamponade due to massive pericardial effusion in pediatric chronic calcific pancreatitis. *J Pediatr Intensive Care*. 2017;06(3):194-198.
9. Hamada S, Masson E, Chen JM, et al. Functionally deficient *TRPV6* variants contribute to hereditary and familial chronic pancreatitis. *Hum Mutat*. 2022;43(2):228-239.
10. Masamune A, Kotani H, Sörgel FL, et al. Variants that affect function of calcium channel TRPV6 are associated with early-onset chronic pancreatitis. *Gastroenterology*. 2020;158(6):1626-1641. e8.
11. Karamouzos V, Karavias D, Siagris D, et al. Pancreatic mediastinal pseudocyst presenting as a posterior mediastinal mass with recurrent pleural effusions: a case report and review of the literature. *J Med Case Reports*. 2015;9(1):110.
12. Oh H-C, Kwon CI, Hajj IIE, et al. Low serum pancreatic amylase and lipase values are simple and useful predictors to diagnose chronic pancreatitis. *Gut Liver*. 2017;11(6):878-883.
13. Habashi S, Draganov PV. Pancreatic pseudocyst. *World J Gastroenterol: WJG*. 2009;15(1):38-47.
14. Sahin-Tóth M. Channelopathy of the pancreas causes chronic pancreatitis. *Gastroenterology*. 2020;158(6):1538-1540.
15. Juanpere S, Cañete N, Ortuño P, Martínez S, Sanchez G, Bernado L. A diagnostic approach to the mediastinal masses. *Insights Imaging*. 2013;4:29-52.

How to cite this article: Tosun SN, Yazol M, Ballıtaş S, Türkyılmaz Z, Boyunaga ÖL. TRPV6 gene mutation associated with giant pancreatic pseudocyst with mediastinal extension in a pediatric patient: Lessons learned. *J Clin Ultrasound*. 2024; 1-4. doi:10.1002/jcu.23823

10970096, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/jcu.23823 by Merve Yazol - Macquarie University , Wiley Online Library on [12/09/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License