Case discussion
acute pancreatitis and Illness Scripts

Antibiotics related acute pancreatitis Causes and management

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Case 1,

- A 64-year-old man presented to our outpatient primary care clinic for an elliptical excision of a skin lesion of the left buttock. There were no immediate complications; however, 8 days after the procedure , he was found to have a surgical site infection. Initially, he was prescribed cephalexin (Keflex) 500 mg 3 times a day, which he took for 4 days prior to transitioning to doxycycline 12 days after the procedure due to an upset stomach.
- The patient was admitted to the hospital 22 days after the procedure (day 10 of doxycycline) with acute onset of epigastric pain radiating to the back, lipase of 6611 units/L, and a CT showing moderate peripancreatic inflammation consistent with pancreatitis. He was diagnosed with pancreatitis and admitted.

急性腹痛而且會轉移到背部,.lipase 明顯增高.而懷疑是急性胰臟炎,這時候醫師應如何找出胰臟炎的原因?

- 先思考胰臟炎最常見的原因,(1)alcohol (2)Gall stone.---(3) procedure related medication,
- His history revealed he had not consumed alcohol recently, and his baseline alcohol consumption was 1 to 2 drinks every other month. He took ibuprofen 800 mg intermittently; the last dose was within 1 week of admission. Doxycycline was taken 12 days after the procedure. Doxycycline was last taken the afternoon prior to admission. He was admitted 22 days after the procedure.
- Doxycycline was taken for 10 days.

- Right upper quadrant abdominal ultrasound showed that the patient's gallbladder was surgically absent, his liver was normal in architecture with no biliary ductal dilation, and the common bile duct was unremarkable with a maximal width of 4 mm. The pancreas was poorly visualized due to overlying bowel gas, and his right kidney was unremarkable. Chest x-ray revealed chronic cardiomegaly with minimal congestion. Past medical history and admission labs are noted As followings.

Past Medical History

- Severe peripheral artery disease with claudication
- Mesenteric ischemia
- Active smoker with 35 pack year history
- Coronary artery disease with prior myocardial infarction, status post 4 vessel coronary artery bypass
- Chronic pain syndrome with bilateral low back pain with sciatica
- Chronic obstructive pulmonary disease
- Stable angina
- Renal artery stenosis
- No history of pancreatitis
- Congestive heart failure with preserved ejection fraction
- Chronic kidney disease stage 3
- No history of alcohol abuse

Presenting Labs

- Complete blood cell count: WBC 15.9/uL, hemoglobin 15.5 g/dL, platelets 214/uL
- Electrolytes (in mmol/L): sodium 145, potassium 3.7, chloride 112, calcium 10.0
- Liver function tests: alkaline phosphatase 112 units/L, AST 13 units/L, ALT 21 units/L, total bilirubin 0.3 mg/dL
- Kidney function: BUN 27 mg/dL, creatinine 1.19 mg/dL, GFR 68 ml/min/1.73 m^2
- Other labs: carbon dioxide 23.0 mmol/L, albumin 3.3 g/dL, troponin 44 ng/L
- Cholesterol panel (in mg/dL): total 106, HDL 48, triglycerides 73, LDL 52

Abbreviations: WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein

病人吃了很多药,到底是不是胰臟炎的原因呢?

Table 2. Patients' Medications, Treatment Duration, Risk of Pancreatitis, Reported Number and Timeline of Development of Pancreatitis

Medications	Evidence Behind Potential Pancreatitis	Patient Duration of Therapy/Literature Reported Time Before Pancreatitis	Number of Reported Cases
Acetaminophen	Case reports, typically with overdose;[5] retrospective cohort study of overdose patients[11]	>17 years/up to 1 year after overdose	13 cases, 1 with reexposure;[5] 2958 cohort and 11 832 controls, HR 2.4 (95% CI, 1.29-4.47)[11]
Albuterol	No reported cases	6 years/NA	N/A
Amlodipine	Case reports FDA medication insert	6 years/time course not provided	<10 cases[5] Between 0.1% and 1%[13]
Aspirin	Case reports	6 years/time course not provided	<10 cases[5]
Atorvastatin	Reported cases; case control study FDA medication insert	6 years/hours to years; OR 1.67 (95% CI, 1.18-2.38) if used within 7 days, OR 1.15(95% CI, 0.87-1.52) if used >7 days ago[10]	2 cases;[12,14] 5810 cases w 5733 controls;[10] <10 cases[5] Frequency not reported[13]
Cistazole	No reported cases	6 years/NA	N/A
Clonidine	Reported cases from 1977; patients had other risk factors including cholestasis and thiazide treatment	6 years/NA	3 cases[15]
Doxycycline	Retrospective cohort study, case studies FDA Medwatch	10 days/2 – 28 days;[1,8,9] 1 case 273 days (chronic use for acne)[1]	4 patients reported across 3 case reports Frequency not defined[16]
Hydrocodone	No evidence for hydrocodone, population-based studies show increased risk of pancreatitis in people who undergo acetaminophen overdose FDA medication insert	>17 years/timeline not provided[5]	N/A[5] Frequency not specified, monitoring patients with known biliary dysfunction is recommended due to concern of sphincter of Oddi spasm[14]
Ibuprofen	Case reports FDA medication insert	>17 years/timeline not provided[5]	<10 cases[5] <1%[13]
Metoprolol succinate	No reported cases	5 years/NA	N/A
Morphine	Possible pancreatitis secondary to morphine overdose;[17] 1 case after routine dose;[18] cited literature for codeine and heroin[5] FDA medication insert	6 years/within 24 hours of initiation[5,17]	2 case reports,[17,18] opiate case reports numbered at 42 with 5 rechallenged[5] Frequency not specified, monitoring patients with known biliary dysfunction is recommended due to concern of sphincter of Oddi spasm[13]
Nitroglycerin	No reported cases	6 years/NA	N/A
Omeprazole	Case reports FDA medication insert	6 years/timeline not provided	<10 cases[5] <1%[13]
Paroxetine	No reported cases FDA medication insert	>17 years/timeline not provided[5]	N/A Frequency not defined[13]
Pregabalin	No reported cases	3 years/NA	N/A

如果是是哪一個呢?

Patient's Calculated Naranjo Score

- 1. 以前是否有關於這種反應的結論性報告？
- 2.不良事件是否在可疑藥物給葯后出現？
- 3.停葯或給予特定拮抗劑后，不良事件是否有所改善？
- 4.給葯時不良事件是否再次出現？
- 5. 是否有其他原因本身可能引起反應？
- 6. 服用安慰劑后反應是否再次出現.?
- 7.在血液或其他液體中檢測到濃度為 +1 的藥物是否已知有毒？
- 8. 劑量增加時反應更嚴重，還是劑量減少時 +1 不那麼嚴重？
- 9.患者在以前的任何接觸中是否對相同或類似的藥物有類似的反應？
- 10. 不良事件是否得到任何客觀證據的證實？

Table 3. Patient's Calculated Naranjo Score[7]

Question	Yes	No	Don't Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	-1
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Total Score				4

Total scores range from -4 to +13. Reactions are considered doubtful if below 0, possible if between 1 and 4, probable if between 5 and 8, and definite if 9 or above. Scores for individual questions are calculated based on specific criteria for each question. See Naranjo et al for specific criteria.[7]

Adverse drug reaction probability scale (Naranjo) in drug induced liver injury. In: LiverTox: Clinical and Research Information on Drug Induced Liver Injury. National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Updated May 4, 2019. Accessed December 8, 2022. https://pubmed.ncbi.nlm.nih.gov/31689026/

Course and treatment-1

- During his hospital course, the patient was allowed nothing by mouth and was treated with intravenous opioids and aggressive fluid resuscitation. His pain improved and he started a clear liquid diet on day 3 of hospitalization; a Patient's Calculated Naranjo Score7 Question
- Reactions are considered doubtful if below 0, possible if between 1 and 4, probable if between 5 and 8, and **definite if 9 or above**.
- 1. ibuprofen were discontinued. On hospital day 4, he was noted to have worsening dyspnea and increasing oxygen requirement. A chest x-ray showed a new right lower lobe infiltrate compared to his admission x-ray, and his white blood cell (WBC) count had increased to 17 400/uL. He was started on cefepime 1g twice daily and vancomycin dosed per pharmacy for aspiration pneumonia. Echocardiogram showed an ejection fraction above 55% and diastolic function with an A wave greater than the E wave.
- On day 5, supplemental oxygen needs decreased.
- On day 6, the patient started a **fat-restricted diet** and was given metronidazole 500 mg 3 times daily due to a persistently elevated WBC count and concern for abdominal infection.
- Repeat abdominal CT scan to evaluate for infection on day 7 showed mild pancreatitis, which was felt to be improving compared to admission CT. He experienced improvement on antibiotics and on a fat-restricted diet during the hospitalization.

Course and treatment-2

- On hospital day 9, the patient was discharged on cefdinir 600 mg daily for 7 days for hospital-acquired aspiration
- pneumonia. On follow-up about 8 weeks after discharge, his primary care clinician indicated he had weaned off his chronic opioids and had some mild, intermittent residual abdominal pain. A lipase checked at this time was normal. Unfortunately, the patient passed away from an acute myocardial infarction about 16 weeks after admission.

Doxycycline-induced pancreatitis previously documented event.

- Chadalavada et al performed a retrospective cohort study looking at 841 cases of acute pancreatitis and found 31 cases secondary to medications, including doxycycline.1
- Additionally, there are several reported probable cases of pancreatitis as a result of doxycycline treatment.

REFERENCES

1. Chadalavada P, Simons-Linares CR, Chahal P. Drug-induced acute pancreatitis: prevalence, causative agents, and outcomes. Pancreatology. 2020;20(7):1281-1286. doi:10.1016/j.pan.2020.07.401
2. Moy BT, Kapila N. Probable doxycycline-induced acute pancreatitis. Am J Health Syst Pharm. 2016;73(5):286-291. doi:10.2146/ajhp150298
3. Shah N, Razzano A, Grendell J. Doxycycline induced severe acute pancreatitis: a rare finding to a common medication. BMJ Case Rep. 2021;14(2):e239640. doi:10.1136/bcr-2020-239640

More common etiologies

1. Such as trauma, ethyl alcohol, hypertriglyceridemia, post ERCP, gallstone disease, and genetic disorders were ruled out via the patient's history.

2. Evaluation for autoimmune and malignant etiologies of his pancreatitis was not pursued due to the lack of typical symptoms (eg, weight loss, jaundice, or pancreatic enlargement), and his clinical improvement. Similarly, viral infections were thought to be unlikely without a history of corresponding symptoms.

3. There was a possibility that the pancreatitis was related to longstanding vascular disease, aspirin, omeprazole, amlodipine, or atorvastatin. However, this was thought to be unlikely due to the temporal correlation of doxycycline treatment.

4. The patient's only medication documented to cause pancreatitis after long-term use was atorvastatin, possibly through interactions with the CYP3A subsystem.19 However, this appears to be a weak correlation, with an odds ratio of 1.67 .Rather than directly causing pancreatitis, it is possible that atorvostatin decreases the threshold for pancreatitis, as it has been noted that **DIP is more likely in patients with multiple comorbidities and polypharmacy.**This is certainly a possibility for our patient given his comorbidities and polypharmacy.

Kaurich T. **Drug-induced acute pancreatitis**. Proc (Bayl Univ Med Cent). 2008;21(1): 77-81. doi:10.1080/08998280.2008.11928366

DIP is rare.

- As in most idiopathic versus DIP cases, it would be difficult to definitively prove doxycycline as the cause without rechallenging, which has obvious ethical concerns. The patient's Naranjo **score was calculated at 4**, indicating a possible reaction
- Furthermore, the time course is within the timeframe of 3 to 15 days reported in several other studies.Not all authors calculated a Naranjo score, so it is more difficult to quantify the likelihood of reaction.We would argue that quantification should be recommended in all suspected cases, due to the difficulty identifying and subsequently diagnosing DIP. Therefore, we argue that with the addition of our case, the Badalov classification for doxycycline would increase to level II within the available literature.
- DIP is a rare etiology of acute pancreatitis, and doxycycline is a medication with case reports supporting it as an inciting etiology. Increasing knowledge of medications with the potential to cause acute pancreatitis will help with diagnostic clarity and therefore elucidate the true incidence and prevalence of drug-induced pancreatitis.

Badalov N, et al :Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol. 2007;5(6):648-644. doi:10.1016/j.cgh.2006.11.023

Classification of Drug-induced pancreatitis(DIP)

Table 1. Classification System of Drug-Induced Acute Pancreatitis

Class Ia drugs
At least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs
Class Ib drugs
At least 1 case report with positive rechallenge; however, other causes, such as alcohol, hypertriglyceridemia, gallstones, and other drugs were not ruled out
Class II drugs
At least 4 cases in the literature
Consistent latency (≥75% of cases)
Class III drugs
At least 2 cases in the literature
No consistent latency among cases
No rechallenge
Class IV drugs
Drugs not fitting into the earlier-described classes, single case report published in medical literature, without rechallenge

(class Ia) are as follows:
mesalamine dipentum (azodisalicylate), bezafibrate, cannabis, carbima zole, codeine, enalapril, isoniazide, metronidazole, pravasta tin, premarin, procainamide, pyritinol, simvastatin, stiboglu conate, sulfamethoxazole, sulindac, tetracycline, and valproic acid.

Class Ib drugs have at least 1 published case showing a rechallenge, but the case failed to rule out other common causes of acute pancreatitis. Class Ib drugs include the fol lowing: all-trans-retinoic acid, alpha methyldopa,

Furosemide: Class Ib There are 5 cases of furosemide-induced pancreatitis that have been reported in the literature.

Azathioprine and 6-Mercaptopurine:
Estrogens: Class Ib ----

class II: acetaminophen, -methyldopa, mesalamine, all-trans retinoic acid, azathioprine/6-MP, codeine,------

Class III: captopril,carbamazepine, ceftriaxone, cimetidine, clarithromycin,

Clkass IV, ampicillin, bendroflumethiazide,benzapril bethamethasone/ roxithromycin, capecitabine, colchicines, cyprohepta dine,danazol,diazoxide,288 diclofenac,289 ergotamine,290 ethacrinic acid,291

Acute pancreatitis and familial hypercholesterolemia

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When Blood Is Thicker Than Water: A Case of Acute Pancreatitis Secondary to Familial Hypertriglyceridemia

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a case of a 56-year-old man with a past medical history of hypertension, diabetes mellitus, and familial hypertriglyceridemia who was diagnosed with acute pancreatitis secondary to hypertriglyceridemia. The patient presented with 9/10 pressure across the abdomen radiating to the sternum. Labs revealed elevated triglyceride count > 8000 mg/dL and cholesterol > 705 mg/dL. Abdominal CT showed fat stranding along the anterior aspect of the pancreatic head. The patient was managed with IV fluids, nil per os (NPO), and statin management for hypertriglyceridemia. Seven days later, triglycerides decreased to 658 mg/dL, and abdominal pain resolved. This case highlights an unusual presentation of acute pancreatitis and demonstrates the importance of understanding the spectrum of etiologies for this condition.