# Biomarker negative pancreatitis caused by Influenza B infection. A case presentation and review of the literature

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## Abstract

***Background:*** *Influenza B is considered to cause milder illness compared to influenza A. There has been no known association between influenza B and acute pancreatitis.* ***Case report:*** *We present a case of an influenza B infection complicated with acute pancreatitis. Furthermore, the biochemical markers that are used to diagnose pancreatitis were normal in this case.* ***Discussion:*** *We present the case that Influenza B can present with severity compared to this of Influenza A. We review the literature on infectious causes and diagnostic criteria for acute pancreatitis and on acute pancreatitis with normal pancreatic enzymes.* ***Conclusion:*** *Influenza B can rarely cause acute pancreatitis. The absence of biochemical confirmation should not exclude the diagnosis of pancreatitis in the appropriate clinical setting.*



## Keywords

*Acute pancreatitis, Influenza B, Normal lipase.*


## Key points

- Influenza B can be associated with significant morbidity and mortality.
- Influenza B can be a rare cause of pancreatitis.
- The absence of elevated amylase and lipase does not exclude pancreatitis in appropriate clinical settings.

## Background

Influenza B is an important human pathogen with prevalence that varies annually; it affects usually younger ages and is associated with milder illness, compared to influenza A. The 2017-18 flu season saw a significant increase in Influenza B prevalence in the UK, with it co-circulating in the community.[1] Although influenza B causes a variety of clinical syndromes, thus far there has been no association with acute pancreatitis. We report the case of a young patient with pancreatitis caused by influenza B, which is - to the best of our knowledge - the first reported case of such an association. Furthermore, the presentation of pancreatitis in this case is unusual, with the biochemical markers that are routinely used to diagnose pancreatitis being within normal limits.

## Case presentation

A 38-year-old male presented to our ED with a plethora of symptoms affecting multiple systems. These included symptoms from the respiratory tract (six days of coryza, sore throat and a productive cough with episodes of haemoptysis), the gastrointestinal track (two days of abdominal pain associated with vomiting with blood content) and constitutional symptoms (several days of fever, myalgia, arthralgia, lethargy and fatigue) as well as a recent acute onset headache with associated photophobia.

His past medical history was unremarkable and he was not known to health services. He was an exsmoker (approximately 20 pack years) having just recently stopped smoking and he was not drinking alcohol. He described a febrile illness in his young son, a few days prior to admission, who had recovered well from it.

He was not on any regular medication. A few days before presentation, he had received Amoxicillin empirically from his primary care physician, which was discontinued after a single dose because of a rash that subsequently resolved. He had also received OTC two tablets of Ibuprofen one day before presentation.

On examination, he was an ill looking young man. Although he was maintaining normal heart rate (85/min) and blood pressure (126/93 mmHg), he was hypoperfused with prolonged capillary refill time (4 seconds) and cool peripheries. His respiratory system examination was unremarkable with a normal respiratory rate (16/min) and oxygen saturation 97% on room air. His abdominal examination revealed

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present bowel sounds and severe epigastric and RUQ tenderness with no rebound or guarding. He was afebrile and there was no peripheral adenopathy and no rash.

## Investigations

Blood studies were mostly normal (FBC, liver enzymes and synthetic functions, urea and electrolytes all within normal range) with the exception of a significantly raised lactate of 5.8 mmol/Lt and a mildly raised CRP of 51mg/L but no leucocytosis. He also had a raised glucose of 12.1 mmol/Lt and a prolonged aPTT of 62.5". His amylase and lipase, triglycerides and calcium were all within normal limits. Venous blood gas analysis revealed a mild metabolic acidosis with pH 7.33 and bicarbonate 22.9mmol/Lt.

The ECG was normal sinus rhythm and the chest X-Ray did not show any consolidation.

## Differential Diagnosis

Based on the available information, a provisional diagnosis of a viral infection (possibly influenza) was considered, Oseltamivir 75 mg BD was commenced and oropharyngeal swabs were taken for viral PCR.

The differentials of pancreatitis (despite the normal biochemical markers) and viscus perforation were also considered, whilst attempting to explain the patient's gastrointestinal symptoms. He was commenced on empirical broad spectrum antibiotics and vigorous intravenous fluid resuscitation and an urgent CT scan of his chest, abdomen and pelvis was arranged.

Despite his physiological parameters being within normal limits, the clinical gestalt was that this young man's physiological reserves were compensating for significant pathological processes and that he was at risk of significant and potentially rapid deterioration.

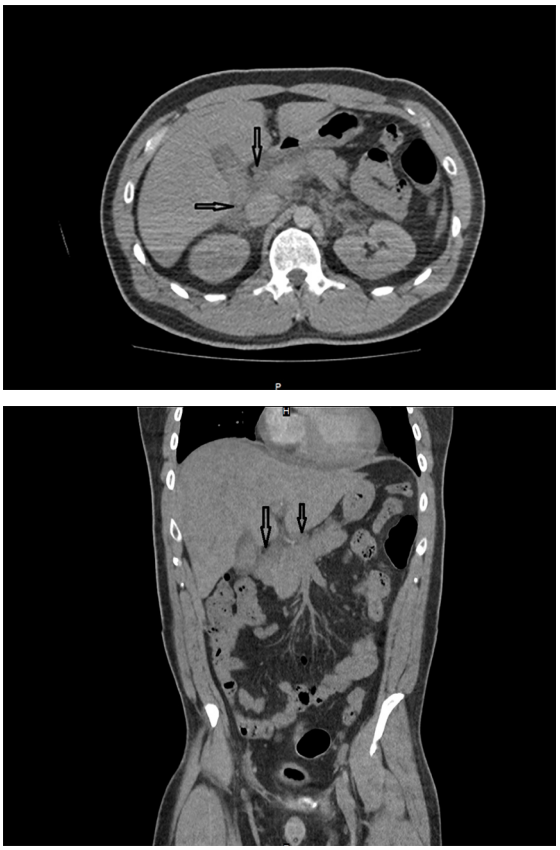
## Management and outcome

The local laboratory PCR testing within a few hours confirmed influenza B infection and was negative for influenza A and RSV. Subsequent testing at the reference laboratory of a Teaching Hospital confirmed the diagnosis of Influenza B infection.

Due to extravasation of the IV contrast medium, the CT scan was without any contrast. It revealed inflammatory fat stranding and free fluid around the head and body of the pancreas, suggestive of acute pancreatitis (Figures 1 and 2); hilar and mediastinal lymphadenopathy and bronchial wall thickening, suggestive of airway inflammation; and a small pericardial effusion. There was no cholelithiasis and the CBD calibre was normal.

Blood cultures did not isolate any pathogen.

Despite vigorous fluid resuscitation there was no clinical or biochemical improvement and within



**Figures 1 and 2.** show the fat stranding and free fluid around the head and body of the pancreas (black arrows), suggestive of acute pancreatitis.

hours the lactate rose to 11 mmol/Lt with evident clinical deterioration. The case was escalated and the patient was admitted to ICU where he sustained a PEA cardiac arrest during intubation and despite one hour of CPR, he unfortunately died.

Post mortem examination revealed an enlarged and swollen pancreas with areas of haemorrhage along the tail, body and head of the organ, consistent with acute pancreatitis. The pancreas was autolytic and no further immunohistochemistry studies were possible. Pancreatic tissue was taken for microbiological and virology studies. The viral PCR of the pancreatic tissue was negative and cultures grew Escherichia coli and Enterococcus, which were deemed by the histopathologist to represent post-mortem contamination and not the cause of pancreatitis. There was no evidence of cholelithiasis. The peritoneal cavity contained 300 ml of cloudy straw-coloured fluid, suggestive of peritonitis. There was fresh blood content in the gastric cavity and gastric mucosa appeared haemorrhagic with small superficial ulcers, representing erosive gastritis.

The respiratory system was revealed to be oedematous with the trachea, bronchi and both lungs appearing congested and oedematous. Examination

of the cardiovascular system revealed mild aortic stenosis and mild left ventricular hypertrophy.

The cause of death was confirmed as acute pancreatitis with peritonitis.

## Discussion

***Influenza B: is it a milder infection?***

Influenza B is an important human pathogen that is usually considered to be affecting younger age groups and to be causing milder symptoms and better outcomes compared to influenza A.[2,3] The prevalence of the infection follows a seasonal variation but its annual circulation is also widely variable. It has been reported that influenza B accounts for an average of 20-25% of the reported cases each year, predominantly amongst children, and rarely only accounts for more than 50% of the total reported influenza cases,[2,3] although large epidemiological data are scarce and limited data exist about its clinical severity and burden on healthcare systems[4]. During the 2017-18 flu season in the UK, influenza B was co-circulating with Influenza A, with significant impact in the older age groups[1] contrary to what was previously reported. Similar observations in the European monitoring network called for a review of the perceived severity of influenza B on individuals and on healthcare systems.[5]

***Influenza B clinical picture***

Influenza A and B infections present with largely similar symptoms and cannot be distinguished based on their clinical features alone. Complicated infections include pulmonary (primary influenza pneumonia[6]) and extra pulmonary manifestations. The latter predominantly affect the heart[7] (myocarditis and pericarditis), connective tissue[8] (myositis and rhabdomyolysis) and less commonly the central nervous system[9] (seizures, Guillain-Barre syndrome, acute disseminated encephalomyelitis and transverse myelitis). Reye's syndrome is a rare complication of Influenza B infection in children and to a lesser degree, it occurs as a complication of influenza A.[6] It has also been reported that gastrointestinal symptoms such as nausea and diarrhoea are more common in influenza B infections.[10]

***Causes of Pancreatitis: viral infections well established***

Infections are well-established causes of pancreatitis and viruses are more likely to cause pancreatitis compared to bacteria, fungi or parasites. Viruses that are most commonly involved in the pathogenesis of pancreatitis include Coxsackie, Hepatitis A, B, C and E viruses, CMV, herpes simplex virus, varicella zoster virus, mumps and HIV[11]. A number of case reports have associated Influenza A with pancreatitis[12,13,14,15,16] and this has called for more studies that would define the association of the two conditions. Capuea *et al*[17] and more recently, Sadeghi et al have demonstrated that Influenza A virus can infect pancreatic tissue and induce pancreatic damage[18] therefore offering some pathophysiological evidence to support this association.

***The association between influenza B and acute pancreatitis***

Despite an extensive review of the literature, we were unable to identify any reports of influenza B associated pancreatitis. Sheikh *et al* have reported a case of pancreatitis that was initially attributed to influenza B but further investigation revealed contamination of the PCR kit.[19] As a result of this experience, the authors of this report have called for increased vigilance when reporting novel disease associations.

The fact that Influenza B was not isolated from the autopsy sample of pancreatic tissue in our case is not unusual and does not exclude the causative association of the two conditions. In their review, Frossard et al report that despite the undisputed role of infections in the pathogenesis of acute pancreatitis, "no microorganism has ever been identified within the pancreas".[20]

In our case, we consider exclusion criteria, epidemiological data and evidence from microbiology studies to support the association of the influenza B and pancreatitis diagnoses. Firstly, there were no other identifiable causes of acute pancreatitis present from the history, the imaging studies or the laboratory investigations. Moreover, the epidemiological and surveillance data confirm that during the period that our patient presented (2017-18 flu season), Influenza B was the co-circulating strain in the community. From all the influenza related ITU/HDU admissions in the UK for that flu season, 52% were influenza A and 48% were influenza B.[1] For comparison, during the adjacent flu seasons the distribution of ITU/HDU admissions was significantly in favour of influenza A (95% influenza A - 5% influenza B for 2016-17 and 99% influenza A - 1% influenza B for 2018-19).[21,22]

Furthermore, analysis of the samples from our patient were conducted independently at two different laboratories, both of which confirmed the diagnosis of influenza B infection. The local microbiology laboratory used the GeneXpert® PCR kit, an assay whose product specification datasheet reports PPA and NPA above 98%[23]. The reference laboratory of the tertiary Teaching Hospital used an in-house developed TaqMan RT-PCR assay. Nucleic acid extraction for the sample was performed using the Biomerieux EasyMAG® system and the assay was run using Qiagen Rotor-Gene Q® system. This assay has been reported to be reliable in the company reported product specification list[24]

and in external independent research.[25] According to the tertiary reference laboratory, the assay's original validation showed sensitivity 100%, specificity 100%, PPV 100% and NPV 100% and continues to perform well in internal and external quality assurance (personal communication).

***Negative biochemical markers pancreatitis***

In our case, the diagnosis of acute pancreatitis is established by use of diagnostic criteria and post mortem findings. The revised JPN clinical criteria for the diagnosis of acute pancreatitis state that the diagnosis of pancreatitis is confirmed when at least two of the following criteria are met: (1) acute pain and tenderness in the upper abdomen; (2) elevated pancreatic enzyme levels in in blood and/or urine; and (3) ultrasound (US), CT or magnetic resonance imaging (MRI) abnormalities of the pancreas characteristic of AP.[26] Our patient met the criteria for the diagnosis (severe epigastric pain and CT findings). Furthermore, the post mortem findings of an "*enlarged and swollen pancreas with areas of haemorrhage along the tail, body and head of the organ, consistent with acute pancreatitis*" confirm the diagnosis, even in the absence of biochemical markers.

It is well established that pancreatitis can present with normal levels of Amylase and it has been proposed that amylase is abandoned as a diagnostic test for pancreatitis[27]. Lipase has been associated with increased specificity for diagnosing pancreatitis and it is exceedingly rare that pancreatitis is diagnosed without significant lipase elevations. However, case reports and case report series exist in the medical literature.[28,29,30,31,32] These cases present a significant challenge in terms of diagnosis and subsequently management as it has been traditionally deemed that a normal lipase level virtually excludes pancreatitis and calls for alternative diagnoses to be considered.[33] Modification of cut-off values for both tests has been suggested as a potential improvement in their diagnostic use.[34] New diagnostic markers are developed and evaluated in the hope that they will improve diagnostic accuracy in suspected cases of pancreatitis.[35]

## Conclusion

This case presented a unique combination: a previously not know disease association (influenza B association with acute pancreatitis) with an exceedingly rare disease presentation (acute pancreatitis without pancreatic level elevation). This report calls for clinical judgement in interpreting the paraclinical investigations in the context of each individual case and consideration of even the rare presentations in the list of differential diagnoses in the appropriate clinical settings.

## Acknowledgements

None

## Conflicts of Interests

No conflicts of interest declared.

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