

*Case report***Clarithromycin associated acute pancreatitis**

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SUMMARY

Drug-induced acute pancreatitis is known to be caused by a wide range of drugs. We report the development of acute pancreatitis, in a previously healthy female, who developed pneumonia and was receiving clarithromycin, at recommended doses. No other cause of pancreatitis could be identified and the patient was not receiving other drugs. Pancreatitis related symptoms and amylase elevation began 2 days after clarithromycin was initiated and resolved after the drug was discontinued. Available case reports that support the possibility of pancreatotoxicity from macrolides, are discussed. Health care professionals should consider this rare, serious, adverse reaction in patients taking macrolide antibiotics.

Key Words: adverse effects, amylase, antibiotics, clarithromycin, drug, pancreatitis, pancreatotoxic, macrolides

INTRODUCTION

The etiology of acute pancreatitis includes gallstones, alcoholism, trauma or endoscopic retrograde cholangiopancreatography, duodenal ulcer, hyperparathyroidism, hyperlipidemia, viral infections and certain drugs.¹ It is estimated that approximately 2% of cases of acute pancreatitis are related to drugs.² More than 250 drugs have been implicated as possible causes of drug-induced pancreatitis.³ Among these drugs, macrolide antibiotics are considered as rare causes. There are reports implicating erythromycin,⁴⁻⁷ roxithromycin,^{8,9} as well as clarithromycin.¹⁰⁻¹²

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We present a case, where a course of clarithromycin, was associated with the development of acute pancreatitis, in an otherwise healthy woman, with community-acquired pneumonia, who was receiving no other drugs.

CASE REPORT

A 36 year-old female, previously in good health, presented to a university medical clinic in northern Greece, complaining of five days of high fever (range 38°-39° C), a paroxysmal, non-productive, cough and a diffuse non-pruritic macular rash. The physical examination demonstrated a febrile, ill-appearing female. The lung examination revealed rhonchi in the upper region of the right lung and the chest x-ray demonstrated the presence of a pulmonary infiltrate, in the anterior segment of the right upper lobe. The diagnosis of community acquired atypical pneumonia was made. Clarithromycin, 500 mg, twice daily, orally, was begun and the patient was hospitalized for closer observation.

The WBC count, on presentation, was $10.6 \times 10^9/L$, with 86% polymorphonuclear cells. The biochemical studies were normal and the serum amylase level was 43 U/l (normal range <90 U/l). Blood cultures, sputum cultures and antiviral serology were not diagnostic and the causative agent could not be identified.

Two days after clarithromycin treatment was initiated, the patient reported mild epigastric pain and nausea. Serum amylase was found to be 184 U/L and serially rose. After four days of treatment, serum amylase was 253 U/l and urine amylase was 3,999 U/l (normal range <613 U/l). The febrile pulmonary infection was in remission. A computer tomography of the abdomen demonstrated an edematous pancreas, without any other abnormal findings. No evidence of gallstones was found. The patient did not have hyperlipidemia, or hypercalcemia, nor did she use alcohol. Furthermore, the patient was on no other medications.

Clarithromycin was discontinued, because it was considered that the acute pancreatitis might have been related to clarithromycin. Within 48 hours, serum and urine amylase levels began to fall and gradually returned to normal. Four days after the drug was discontinued, the patient was discharged from the hospital. Two weeks later, when the patient was re-examined, she was feeling well and had normal levels of serum and urine amylase.

DISCUSSION

The patient presented with none of the well-known causes of acute pancreatitis. The symptoms of acute pancreatitis and the rise of amylase levels, occurred after the administration of clarithromycin and resolved after the drug was discontinued, suggesting a causal association, particularly since the patient had not received any other drug except clarithromycin.

Clarithromycin is an effective, widely used drug in community-acquired pneumonia. Post-marketing, there have been a small number of reported cases of acute pancreatitis, possibly induced by clarithromycin.¹⁰⁻¹² This has prompted the companies that manufacture the drug to include pancreatitis among the list of rare adverse reactions (occurring in <1%) in drug monographs. To our knowledge, this is the first reported case of acute pancreatitis associated with clarithromycin administration, in Greece.

The mechanism by which macrolides cause pancreatitis is not clear. It has been proposed to involve direct cellular toxicity, or, that there is a direct effect on smooth muscle fibers of the intestine and that this causes spasm of the sphincter of Oddi and bile reflux.^{7,13,14} Others have suggested it is an immune mediated reaction.^{4,6}

Definite conclusions about adverse drug reactions causing acute pancreatitis are often difficult to make, because of several factors, that include the co-existence of a potentially pancreatotoxic disease, the use of multiple drugs, and the lack of drug re-challenge data. Our patient was previously healthy, her only disease was pneumonia and she was not taking any other medication. We did not re-challenge the patient with clarithromycin, for ethical reasons and also, because the patient refused. The Naranjo acute drug reaction probability scale, used to assess the likelihood that a disease is drug related, revealed a probable adverse reaction (score= 6 out of 10).¹⁵

Infections are considered to be rare causes of pancreatitis and viruses are mainly implicated (coxsackievirus, cytomegalovirus, echovirus, mumps).¹ In our patient, viral serology was negative. Nonetheless, the possibility that the

pancreatitis was caused by an infectious agent, that also caused the febrile pulmonary infection and the rash, cannot be definitely excluded. However, pancreatitis appeared at the time the febrile pulmonary infection was in remission and only began to resolve after the drug was stopped.

This case report, is very similar to the first report of pancreatitis induced by clarithromycin, by Liviu, et al., that also occurred in a previously healthy, adult, female with pneumonia.¹⁰ Many other available reports, that refer to acute pancreatitis, associated with post-erythromycin macrolides, involve patients with previous medical problems and/or patients receiving multiple drugs, thus raising some questions about the role of the macrolide.^{8,11,12,16}

The disease in our patient had a benign course and was reversible after the drug was discontinued. This is in agreement with most other reports of drug-induced pancreatitis, involving new macrolides.⁸⁻¹¹ However, one death has been reported following a course of clarithromycin and a second death, may have been associated with a course of azithromycin.^{12,16} Both patients, had serious medical problems and were receiving more than one potentially pancreatotoxic drug (chlorthalidone and clarithromycin in the first case, valproic acid and azithromycin in the second). Importantly, the drug was not stopped during hospitalization and the diagnosis of drug-induced pancreatitis was suspected after the postpartum autopsy showed severe acute pancreatitis.^{12,16}

Since macrolides are widely used drugs, particularly in the outpatient medical practice, physicians should consider the possibility of this rare, serious, adverse reaction.

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