

## Nifuroxazide-induced acute pancreatitis : a new side-effect for an old drug ?

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### Abstract

We report the case of a middle-aged woman who developed a typical picture of acute pancreatitis together with systemic features of immunoallergy after the intake of two capsules (200 mg) of nifuroxazide. Even if acute pancreatitis is a rare adverse event of nitrofurantoin therapy, nifuroxazide-induced pancreatitis as not been previously described. As suggested by associated systemic features, the disease is likely of immunoallergic origin. (*Acta gastroenterol. belg.*, 2007, 70, 32-33).

**Key words :** pancreatitis, drug-induced, nifuroxazide.

### Introduction

Drug-induced acute pancreatitis accounts for about 1.4-2 % of all cases of pancreatitis (1). A large number of drugs have been implicated mainly azathioprine, thiazides, furosemide, valproic acid, H<sub>2</sub>-receptor antagonists, tetracycline, sulfonamides and a number of others (4,5,6), even if strong arguments for causality have been obtained only for a minority (8,9). The pathogenesis of drug-induced pancreatic injury remains ill-defined ; the main mechanisms likely involved include a toxic metabolic injury, pancreatic duct constriction or hypersensitivity (7).

To our knowledge, there has been no previous report of acute pancreatitis associated with the use of nifuroxazide, a medication which remains widely used in the treatment of diarrhoea suspected to be of infectious origin (10). We report the case of a patient who developed clinical biochemical and morphologic features of acute pancreatitis together with fever and skin rash after the administration of two capsules of the medication.

### Case report

A 56 year-old woman was admitted to the emergency unit of our Hospital with fever, epigastric pain and pruritus related to a maculo-papular eruption appeared two hours after the intake of 2 capsules of nifuroxazide (200 mg) for atypical intestinal symptoms referred to as "abdominal discomfort".

Her past medical history was unremarkable. She had no history of alcohol abuse and had only been taking alprazolam (0.25 mg/day) and paroxetine (20 mg/day) for years.

At physical examination there was a maculo-papular eruption on the chest, arms and legs. The abdomen was not distended. Epigastric tenderness was noticed at abdominal examination.



Fig. 1. — Tomographic appearance of the upper abdomen showing a diffuse oedematous enlargement of the pancreas (arrows).

Biochemical features included CRP : 54 mg/dl (0-10), eosinophils : 1.8% (0-6%) rising at 10% (720/mm<sup>3</sup>) on day 6, liver function tests being all in the normal range. Blood calcium was at 8.6 mg/dl (8.5-10.5) at admission together with an increase in amylase at 362 IU/L (N : 1-100) and lipases at 719 IU/L (16-60).

Serological testing for Hepatitis A, B and C ; HIV, Herpes, CMV, EBV were all negative. Auto-antibody determinations including antinuclear and anti-neutrophils cytoplasmic antibodies as well as the rheumatoid factor were negative.

Fasting upper abdominal ultrasound showed a normal appearing gallbladder without dilatation of the biliary tree and the common bile duct. Abdominal computed tomography showed a diffuse pancreatic oedema compatible with an acute pancreatic inflammation (Fig. 1).

Following admission, a diagnosis of mild acute pancreatitis with a Ranson's score of 2 was made. A cutaneous biopsy was performed which showed a picture of vasculitis (Fig. 2) with C3 complement fraction deposit at immunofluorescence examination.

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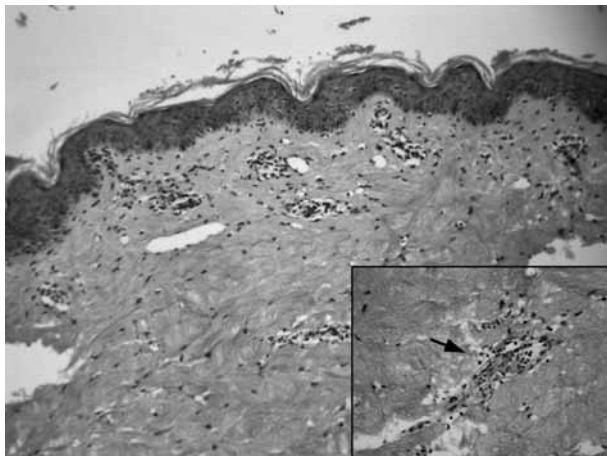


Fig. 2. — Histopathological picture of the skin biopsy showing a mild perivascular infiltrate, mainly lymphocytic with a few neutrophils (arrow).

A conservative treatment including a light diet together with an antihistaminic preparation (levocetirizine : 5 mg per day) resulted in a slow clinical and laboratory improvement. The patient was released on day 11 in good physical condition and the eruption had disappeared.

## Discussion

A case of acute oedematous pancreatitis occurring two hours after the intake of 400 mg of nifuroxazide is reported and this, together with rash and hypereosinophilia, both suggestive of an immunoallergic type of toxicity. This was further confirmed by histological examination of a skin biopsy which revealed a non specific picture of vasculitis as sometimes seen in drug-induced adverse reactions (11).

In addition to the absence of another cause of pancreatic disease, the criteria for the diagnosis of drug-induced pancreatitis generally include the fact that pancreatitis develops during treatment, resolves upon discontinuation of the drug and recurs after rechallenge (12). In our case and even if the last criteria was not fulfilled, the fact that the disease was associated with well documented systemic immunoallergic features appears as a strong argument in favour of a drug-induced pancreatitis and also in favour of its idiosyncratic, immunoallergic origin.

Nifuroxazide has been used since 1963 for the treatment of infectious diarrhoea. Reported side effects of the drug include nausea, vomiting, fever and skin rash.

The fact that the medication might be responsible for drug-induced pancreatitis is not entirely unexpected since nifuroxazide shares chemical similarities with the nitrofurans, some of which having been implicated in the occurrence of rare cases of pancreatitis (2,3).

Among medications implicated in the occurrence of pancreatitis, evidence of causality was provided only for

Table I. — Drugs for which a causality between intake and pancreatitis has been documented

<ul style="list-style-type: none"> <li>– 2',3'-dideoxyinosine (Lankisch, Droge, and Gottesleben, 1995)</li> <li>– Azathioprine (Underwood and Frye, 1993 ; Lankisch, Droge, and Gottesleben, 1995 ; Eland <i>et al.</i>, 1999 ; Andersen, Sonne, and Andersen, 2001)</li> <li>– Furosemide, frusemide (Underwood and Frye, 1993 ; Lankisch, Droge, and Gottesleben, 1995)</li> <li>– Metronidazole (Eland <i>et al.</i>, 1999)</li> <li>– Oestrogens (Underwood and Frye, 1993 ; Lankisch, Droge, and Gottesleben, 1995)</li> <li>– Pentamidine (Underwood and Frye, 1993)</li> <li>– Tetracyclines (Underwood and Frye, 1993)</li> <li>– Thiazides (Underwood and Frye, 1993)</li> <li>– Valproic acid/valproate (Asconape <i>et al.</i>, 1993 ; Underwood and Frye, 1993 ; Andersen, Sonne, and Andersen, 2001)</li> </ul>
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a minority of compounds (8,9) which are listed in table I. The mechanisms involved in the pathogenesis of pancreatic inflammation remain unknown. In addition to an immune-mediated inflammatory response as observed in our case, they include hypertriglyceridemia, metabolite-related injury of the pancreas (i.e. free radicals) and pancreatic duct constriction (7).

In conclusion, we have reported the history of a patient who developed a clinical, biochemical and radiological picture of acute immunoallergic pancreatitis following the intake of a small dose of nifuroxazide, a drug of rather low therapeutic impact whose chemical structure shares similarities with that of nitrofurantoin. Associated features were in favour of an immuno-allergic type of toxicity. Clinicians should be aware of this newly documented potential side-effect of the drug.

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