Monascus ruber: invasive gastric infection by dried and salted fish consumption

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We report a case of invasive gastric infection caused by *Monascus ruber* observed in a patient from French Guiana with gastric adenocarcinoma. The originality of this case is because, firstly, this invasive mycosis is extremely rare and secondly, the probable mode of infection was by the consumption of *Monascus ruber*-contaminated food.

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**CASE REPORT**

In July 2003, a 66-year-old man was hospitalized in Cayenne hospital, French Guiana, with a history of chronic cough for seven months, dyspnea, asthenia, anorexia, gastro-esophageal reflux, constipation, intermittent fever and calf pain. He lived in the vicinity of Grand Santi, a village located on the French side of the Maroni River, in the East of French Guiana. Except for a high tobacco consumption for 45 years, he had no notable medical antecedents. At the time of admission, the results of pulmonary, cardiovascular and abdominal clinical examinations were normal. The patient was in good general state without fever. Abnormal laboratory findings included normochromic normocytic anemia (hemoglobin 9.8g/dL) and an increase in C-reactive protein (97mg/mL with N<5mg/mL). Other biologic data were within the normal range.

An abdomino-pelvic ultrasound revealed celiac and mesenteric lymphadenopathy, without other anomalies. Abdominal tomography showed considerable gastric distension with stasis, associated with antral tissue hypertrophy. Given these results, endoscopy was carried out. Gastric and duodenal biopsies were performed and duodenal liquid was aspirated for analysis. Duodenal biopsies showed interstitial duodenitis and histological analysis of the
gastric biopsies revealed moderately differentiated gastric adenocarcinoma associated with chronic gastritis, extensive metaplasia and massive bacterial superinfection, including *Helicobacter pylori*.

Septated, wide, and banded fungal filaments, with right angle branching were observed in the gastric biopsies with Gomori-Grocott and periodic acid-schiff (PAS) stains. The pathologist has first concluded that there was a fungus from the Mucoracea family.

Fungal cultures were carried out with fragments of the gastric biopsies and duodenal liquid on gentamicin-chloramphenicol Sabouraud medium with or without cycloheximide at 30°C and 37°C. Two fungi were isolated from the biopsies at 30°C and 37°C: a Mucoracea without sporulation on the two fungal media and a white to purple fungus with a dull reddish pigment on the reverse side of the culture plate on the Sabouraud medium without cycloheximide. The growth of the second fungus was rapid and the colonies were thinly floccose, spreading from the middle (Fig A). The microscopic examination of the culture were positive for *Monascus ruber* (anamorph: *Basipetospora rubra*), a fungus with distinctive characteristics as described below: chains of round and colorless conidia (9-10.5µm/7-9µm) with flattened bases (Fig B1), and young round thin-walled ascospars containing oval ascospores with smooth walls (5-6µm/4-5µm) (Fig B2). The Mucoracea and *M. ruber* were also isolated from the duodenal aspiration liquid, associated with *Candida glabrata*.

The histological slides of the gastric biopsies were then carefully re-examined and the morphological characteristics of 2 types of fungi were recognized confirming the presence of *M. ruber* in the biopsies (Fig C1 and C2).

Treatment with amphotericin B, 50mg per day was initiated. Three days later, because of nephrotoxicity (the creatinine increased from 88 to 150µmol/L), amphotericin B was switched to the liposomal form, 200mg per day. Five days later, the dose was decreased (200mg one every other day) because of an increase in kidney failure.
The origin of this atypical infection was researched and an alimentary cause was suspected. The patient was a high consumer of fish, principally dried and salted. Fungal cultures were carried out on the remains of salted fish (*Serrasalmus rhombeus* called *pêne*) found in his room at the hospital and consumed by the patient during his hospitalization. The skin, the flesh and the salt were cultured separately at 30°C and 37°C on the previously-used media. The salt and flesh cultures were positive for *Monascus ruber*, only on Sabouraud medium without cycloheximide at 30°C and 37°C, but the skin was negative.

The surgical treatment of the gastric adenocarcinoma was not possible because of a deterioration of the patient's general condition and extensive venal thrombosis of the inferior left member.

A second control gastric biopsy was taken 45 days after the first one (after 5 weeks of treatment). The direct examination showed the same fungal elements and *Monascus ruber* was isolated alone from culture at 30°C and 37°C. After this, the patient was released and returned back home, where he died shortly after.

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*Monascus ruber* (anamorph: *Basipetospora rubra*) is a filamentous fungus (family Monascaceae, order Eurotiales) (16). This Ascomycete has rarely been implicated in human infection (13). We report here an uncommon case of *Monascus ruber* invasive gastric infection associated with the consumption of contaminated dried and salted fish.

In Asia, this fungus is traditionally used to produce *Monascus*-fermented rice and is commonly employed as food colorant, flavoring agent or additive for preserving fish and meat (14). In industry, *Monascus* species are important sources of pigments or bioactive compounds (8), like monacolin K which is a very effective hypocholesterolemic agent (4).
In humans, *Monascus* can be pathogenic in several ways: i) allergy and anaphylaxis to red yeast rice have been described (6), due to an immediate sensitivity to *Monascus purpureus*. ii) toxicity: some *Monascus* compounds are toxic, such as citrinin which is a nephro-hepatotoxic agent (7). Citrinin permeates into the mitochondria where it alters Ca2+ homeostasis (2) and interferes with the electron transport system (12). Moreover, a toxic drug interaction was also reported between cyclosporine and monacolin K of the red yeast rice (*Monascus purpureus*) that led to a rhabdomyolosis in a renal transplant recipient (11). iii) infection: one study described a direct renal infection after surgery due to *Monascus ruber* in a 70 year old patient with multiple kidney stones (13). Our report is the second description of *Monascus ruber* infection world-wide with tissue invasion and the first case where an alimentary contamination was highlighted. The presence of the fungus in the histological tissue of the gastric biopsies demonstrated the invasive capacity of this mycosis.

*Monascus ruber* is a salt and acid tolerant fungus (10). At 35°C (approximate gastric temperature), the lower pH limit permissive of *Monascus* growth is 3.7 but the development of the fungus is further promoted when the pH rises to neutral (10). In a healthy stomach, the very low pH of 1-2 should not allow the proliferation of the fungus. Functional alterations of the stomach (dyspepsia), associated with an increase in the gastric pH, may be one of the factors favoring this infection. As *Monascus ruber* is NaCl tolerant, it was not surprising to find *Monascus ruber* in the dried and salted fish. *Monascus* had already been isolated from dried and salted fish in Sri Lanka (1), Indonesia (15) and Nigeria (3) or from green table olives (9) but food contamination in man has never been observed.

After the treatment with amphotericin B and the liposomal form, nephrotoxicity developed whereas the patient's renal function was normal at admission. It is possible that this toxicity was the consequence of not only amphotericin B, but also of the citrinin, produced.
during the lyses of the fungus (5, 7). Thus, it would be preferable to use an antifungal drug without nephrotoxicity to avoid the possible potentiation of renal failure by citrinin.

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REFERENCES


**Figure legend**

**Fig:** *Monascus ruber.* (A) Macroscopic aspect with red pigment after growth on Sabouraud’s agar medium for seven days at 37°C. Microscopic characteristics of the isolate of *M. ruber* with two types of reproduction: (B1) asexual form with a chain of conidia (magnification, x 200) and (B2) sexual form with thin-walled ascoscarps containing ovals ascospores (magnification, x 400). Histological microscopic examination of a gastric biopsy (magnification, x 400): (C1) Gomori Grocott stained area of tumor necrosis with truncated fungal filaments (red arrows) and (C2) PAS stained with banded fungal filaments branched at right angles characteristic of a Mucoracea fungus (yellow arrows) and wide vesiculated septate filaments (blue arrows) characteristic of *Monascus.*
Figure