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CASE REPORT

Malignant tumor-like gastric lesion due to *candida albicans* in a diabetic patient treated with cyclosporin: a case report and review of the literature

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Abstract The gastrointestinal tract of healthy individuals is colonized by hundreds of saprophytes and mycetes, especially the *Candida* species, are habitual ones. Under certain conditions, the fungal flora may overgrow, resulting in lesions of the digestive mucosa which, rarely, can have a local diffusion and/or spread to the lympho-hematogenous system. Mycotic infections of the stomach can sometimes look like benign gastric ulcers. Here, we present the case report of a woman, aged 64, who presented with type II diabetes mellitus and psoriasis, on chronic treatment with cyclosporin A and with endoscopic evidence of an ulcerated, vegetating gastric lesion secondary to *Candida albicans* infection. Although strongly suggestive of malignancy, it completely healed after cyclosporin withdrawal and the administration of oral antifungal drugs.

Keywords Candidiasis · Mycotic infection of the gastrointestinal tract · Submucosal tumor

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Introduction

The digestive tract is colonized by hundreds of saprophytes including mycetes, especially the *Candida* species [1, 2]. Mycotic infections of the gastrointestinal system are rare and usually involve the upper digestive tract. Nevertheless, under certain conditions, fungal flora may overgrow, resulting in lesions of the digestive mucosa, which can, rarely, have a local diffusion and/or spread to the lympho-hematogenous system. The most important risk factors are the following: (1) the administration of antibiotics, steroids, immunosuppressive and anticancer drugs; (2) gastrointestinal diseases, such as eosinophilic gastritis, cancer (i.e., lymphoma), Zollinger-Ellison syndrome and Crohn's disease; (3) systemic diseases, such as tuberculosis and polyarteritis nodosa; (4) smoking. Mycotic infections of the stomach can sometimes look like benign gastric ulcers. This relationship has been repeatedly reported in the literature, but never clearly demonstrated [3–6]. We report the case of a woman, aged 64, who presented with type 2 diabetes mellitus (DM) and psoriasis, on chronic treatment with an immunosuppressive drug such as cyclosporin A and with endoscopic evidence of an ulcerated, vegetating gastric lesion secondary to *Candida* (*C.*) *albicans* infection. Although strongly suggestive of malignancy, the lesion completely healed after cyclosporin withdrawal and the administration of oral antifungal drugs.

Case report

In August 2010, a 64-year-old woman was admitted to our Department for epigastric pain and melena. Furthermore, she reported anorexia and a weight loss of 5 kg over the previous 3 months. In 1990, she had been diagnosed with

psoriasis and had been treated with cyclosporin A since 2003. She was also receiving metformin treatment for type 2 DM and acetylsalicylic acid (ASA) for a previous myocardial ischemia. Clinical examination showed severe epigastric pain, cutaneous pallor and psoriatic lesions mostly localized to the sacrum and nails. Laboratory tests showed hypochromic microcytic anemia (hemoglobin concentration 8.3 g/dl; n.v. 12–17), with hyposideremia (3 μg/ml; n.v. 40–200) and hypoferritinemia (7 ng/ml; n.v. 15–300). Endoscopic examination of the upper digestive tract revealed a multi-ulcerated vegetating lesion greater than 5 cm in size on the posterior wall of the stomach body, which was affecting the progression of peristaltic waves (Fig. 1). The ulcers showed irregular margins and fibrinous bottoms. Although these findings were strong clinical evidence of a malignant gastric lesion, biopsies of the ulcers and of the vegetating lesion revealed only a marked chronic inflammatory infiltrate with moderate activity, associated with degenerative-necrotic phenomena. The patient was therefore discharged, given proton pump inhibitors (PIPs) and advised to undergo endoscopy and histology follow-up.

Three weeks later, the patient was re-admitted to our Department and another endoscopy of the upper digestive tract showed an unchanged ulcerated vegetating lesion on the posterior wall of the stomach body. Multiple biopsies showed chronic gastritis with generally moderate activity, but locally severe, and areas of foveolar hyperplasia. CT scan with contrast medium of the chest and abdomen revealed a 7-mm nodular lesion in the medial segment of the right middle lobe of the lung of unknown origin and irregular thickening of the posterior wall of the stomach body. This was associated with hyperplastic lymph nodes along the lesser curvature of the stomach, in the liver hilum and celiac, portacaval and inter-aorto-caval regions, as well as splenomegaly (Fig. 2). The patient was discharged and then admitted to the Surgery Department of our Hospital, where a new upper digestive tract endoscopy showed evidence of the same lesion which now extended to the stomach body and antrum. At this time, however, biopsies showed chronic gastritis, with moderate activity and degenerative-necrotic phenomena, and a great quantity of *C. albicans* hyphae in the inflammatory exudates (Fig. 3). On this basis, cyclosporin was withdrawn and oral itraconazole treatment commenced (100 mg b.i.d. for 15 days, then repeated after 15 days of suspension). After 6 weeks, the patient's symptoms disappeared, body weight increased by 3 kg and anemia improved (hemoglobin concentration 10.8 g/dl). Two months later, endoscopy showed a significant volume reduction in the vegetating and ulcerated stomach lesion (Fig. 4), while CT scan with contrast medium of the chest and abdomen showed the complete disappearance of the gastric thickening, abdominal lymph nodes and the nodular lung picture. Further upper digestive tract endoscopy after 6 months revealed the complete disappearance of the lesion.

Discussion

Even though mycetes are habitual saprophytes in healthy subjects, candidiasis is the most frequent fungal infection of the gastrointestinal canal. *Candida* has been described in oropharynx, jejunum, ileum and stool samples [7]. Not only immunocompromised patients may suffer from *Candida* infections, but even apparently healthy subjects [8]. The esophagus is the area most usually involved, and infection is

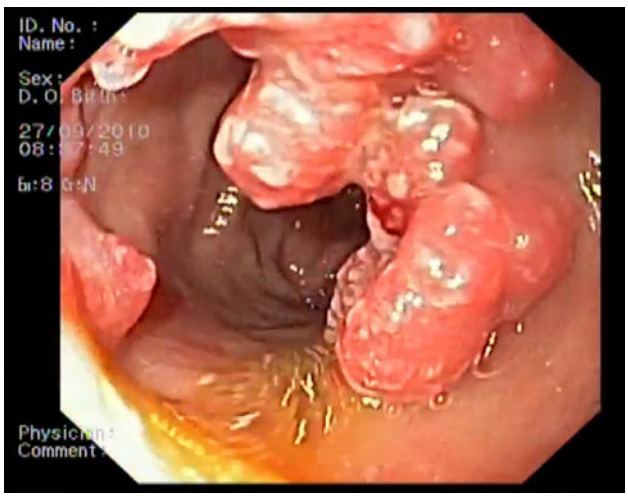

Fig. 1 Endoscopic appearance of a multi-ulcerated vegetating lesion, with circumferential pattern, >5 cm in size, on the posterior wall of the stomach body. Ulcers presented with irregular *margins* and fibrinous *bottoms*

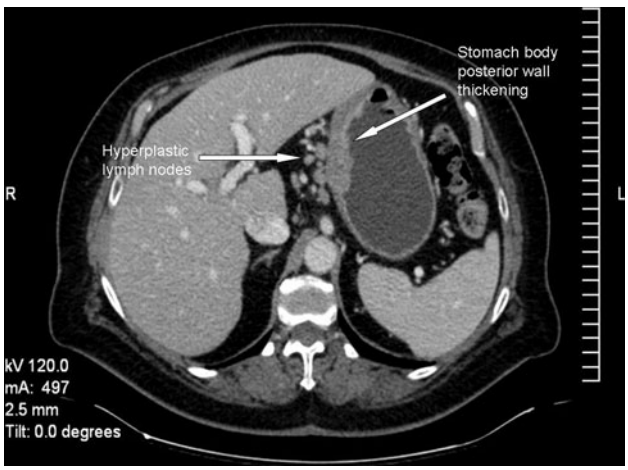

Fig. 2 CT scan of irregular thickening of the posterior *wall* of the stomach body, associated with hyperplastic lymph nodes along the *lesser* curvature of the stomach, liver hilum and celiac, portacaval and inter-aorto-caval regions, as well as splenomegaly

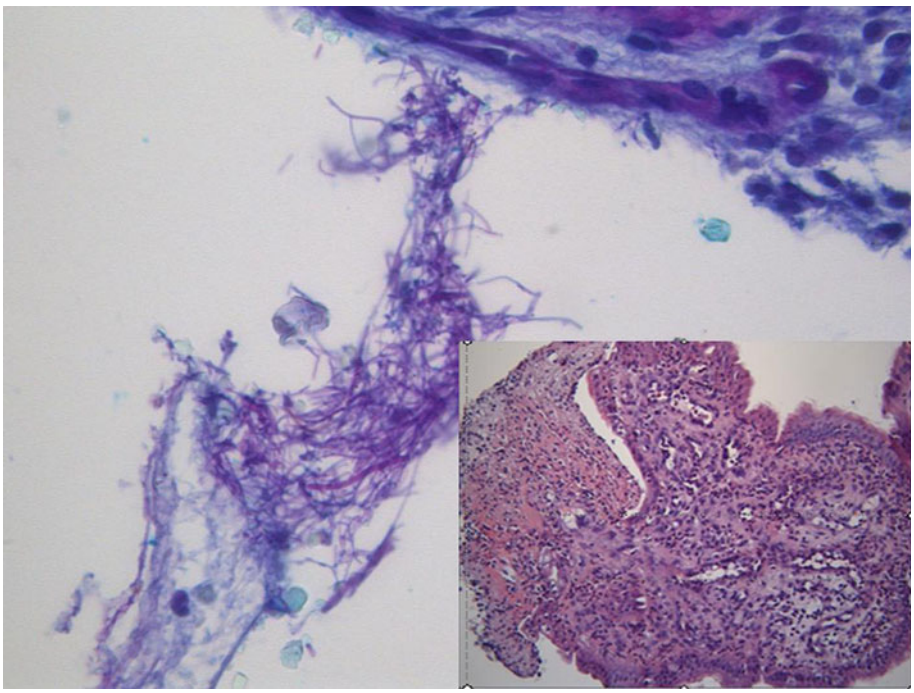

Fig. 3 Histology of the gastric lesion, showing chronic gastritis, with moderate activity and degenerative-necrotic phenomena (hematoxylin and eosin staining), and numerous *Candida albicans* hyphae, positive for Alcian *Blue* and Periodic Acid-Schiff (PAS) staining, in the inflammatory exudate

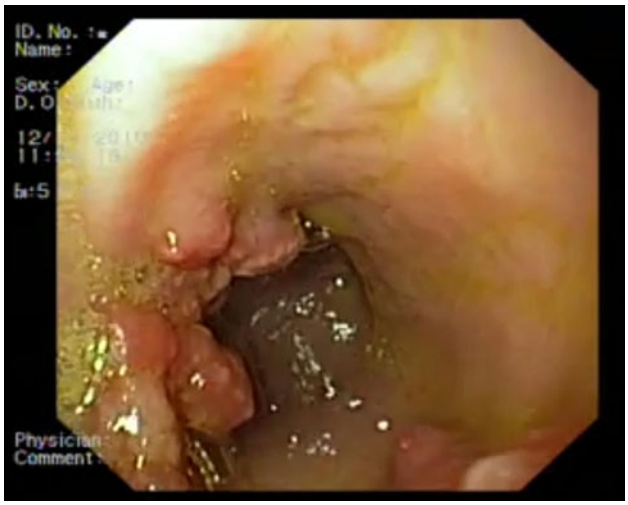

Fig. 4 Endoscopic appearance of the significant *volume* reduction in the vegetating ulcerated stomach lesion after 2 months of itraconazole therapy

associated with odynophagia, dysphagia and bleeding. The stomach, despite its extremely acid environment, may also be affected, showing diffuse mucosal involvement or, occasionally, a focal invasion and colonization of benign gastric ulcers [9, 10].

Autopsy studies have shown an estimated prevalence of fungal infection in the gastrointestinal tract of 4% in deceased cancer patients. Prospective studies have demonstrated an esophageal localization in 2.5–7.3% of patients who had undergone endoscopy, as well as a fungal infection in 16% of benign gastric ulcers and in 18% of stomachs resected for gastric ulcers. These data suggested that a benign gastric ulcer associated with an overlying *Candida* infection is not uncommon [3, 7, 11, 12].

The high prevalence of gastrointestinal fungal infections might be explained by a decreased immunological competence and an increased incidence of systemic diseases (especially DM and malignancies), as well as by the increased use of anti-H2 receptors or PPIs which, by altering the acid gastric environment, may promote overgrowth of the physiological mycotic flora [13–15]. The stomach fundus is mainly affected by benign infection gastric ulcers, perhaps because it is the most common site for benign gastric ulcers. Endoscopy findings of *Candida*-infection gastric ulcers vary from ulcerated lesions with indented borders to submucosal tumor-like lesions, bezoar-like images, gastric foreign bodies and very large lesions (>2 cm) [16–18].

There are few reported cases of bleeding or perforation caused by *Candida*-infection gastric ulcers, and therapy should be commenced as soon as possible [19–22]. Treatment modalities include anti-H2 receptors/PPIs or antifungal drugs, or a combination of both, but well-defined guidelines have not yet been established. Antifungal treatment seems to be unnecessary in young patients without severe underlying diseases, since most of these have been reported to recover without specific treatment. Antifungal drugs may be considered either in high-risk patients (advanced age, use of immunosuppressive drugs, malignancy), where elevated fungal proliferation may cause local complications (bleeding and/or perforation), the systemic spreading of mycetes or colonized ulcers

unresponsive to treatment with anti-H2 receptors and PPIs [23, 24].

To our knowledge, this is the first report of an ulcerated vegetating gastric lesion strongly suggestive of malignancy, in which *Candida* etiology was clearly proven by the failure of the standard therapy with anti-H2 receptors and PPIs and by the complete response to the antifungal therapy and the suspension of the immunosuppressive drug. The infection, as described in the literature, occurred in a high-risk adult immunosuppressed patient with type 2 DM and on chronic treatment with cyclosporin for psoriasis [3, 4].

Digestive mucosal immunity to *C. albicans* depends on multiple immune components, i.e., CD4+ and CD8+ cells and polymorphonuclear leukocytes (PMNs), and nonimmune cells, such as oral keratinocytes, epithelial cells and stromal cells. However, both experimental and clinical data are consistent with a central role for T cells in the host response against gastrointestinal candidiasis, represented by T_H1 cytokine profile expression by CD4+ cells (i.e., production of IFN-γ), without demonstrable T_H2-like response. Moreover, interactions between T cells and PMNs are required to keep host defense to *Candida* infection running. IL-17-mediated regulation of neutrophil expansion, recruitment and migration allows T_H17 cells, activated by CD4+ cells, to also modulate the PMNs response [25–27].

Patients affected with type 2 DM have more infections than not affected ones. Course of infections is also more complicated in the firsts. One of the possible causes of this increased infections prevalence is a defect in immune responses. Concerning adaptive immunity, it has been demonstrated a T_H2-axis shift, which reduces T_H1-dependent immunity. Other faults (e.g., low complement factor 4, decreased cytokine response after stimulation) in humoral innate immunity have been described in diabetic patients. Regarding cellular innate immunity, most studies showed decreased functions (chemotaxis, phagocytosis, killing) of diabetic PMNs and monocytes/macrophages compared with controls ones [28]. In addition, DM represents an important contributory factor in digestive candidosis. Several pathogenic mechanism have been hypotized to explain the higher risk of digestive mucosal infection by *Candida* in DM patients: high salivary glucose levels, which favor yeast growth; glycosylation products with proteins on buccal epithelial cells during hyperglycemic episodes, that may increase the number of available receptors for *Candida;* decrease in salivary flow rate, sometimes described in DM patients, which may further enhance *Candida* colonization, by reduction in immunoglobulin A and free secretory component levels, which normally inhibit *Candida*; and finally, decreased phagocytosis, intracellular killing, bactericidal activity and chemotaxis of PMNs, associated, particularly, with poorly controlled diabetes, that may render the diabetic patients more susceptible to *Candida* infection [29].

Cyclosporin A effectively suppresses T-cell-dependent immune reactions, binding together with cyclophilin, a cytoplasmic receptor protein present in T lymphocytes, and this complex further hitches to calcineurin and inhibits Ca^{2+}-stimulated dephosphorylation of the cytoplasmic component of the nuclear factor of activated T cells (NFAT), thus inhibiting translocation of NFAT from cytoplasm to nucleus of activated T cells, and therefore, T cells function. Considering the role of CD4+ and CD8+ T cells in the development of an effective immune response to mycetes, i.e., *Candida*, it is possible that impairing of adaptive immunity may be co-responsible for *Candida* overgrowth and the histopathologic findings of our high-risk patient for fungal infections [30, 31]. The malignant tumor-like characteristics of the lesion may be due to inflammation and cell infiltration in the deep mucosal layer, which completely healed after antifungal treatment, as did the hemorrhagic complication of the lesion (iron deficiency and sideropenic anemia) and its loco-regional (circumferential gastric wall involvement *plus* abdominal lymph node colonization) and probably systemic (pulmonary) diffusion.

In conclusion, this case report suggests that in a high-risk patient for fungal infections a benign gastric lesion, albeit with malignant tumor-like characteristics, may indicate the possibility of *Candida* infection and consequent specific antifungal treatment.

Conflict of interest None.

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